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VOLUME 33 NUMBER 5

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PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

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Archives of Internal Medicine

VOL. 33 MAY, 1924 No. 5

PARADOXICAL SHORTENING OF THE COAGULATION TIME OF THE BLOOD AFTER INTRAVENOUS ADMINISTRATION OF SODIUM CITRATE *

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NEW YORK

Sodium citrate renders blood incoagulable when the two are mixed in proper proportions in the test tube. Because of its well-known anticoagulant action, it was first employed for blood transfusions in this country by Lewisohn [1] and by Weil,[2] and abroad by Hustin [3] and Agote.[4]

In 1915, while working with Lewisohn [1] on some of the preliminary experimental work, one of us (G. B.) observed a remarkable and apparently paradoxical shortening of the coagulation time of the blood in human beings and dogs following transfusion of the citrated blood. The effect was strikingly brought out in one of these experiments. Blood taken from a dog before a citrate transfusion showed a clotting time of five minutes. Three hundred cubic centimeters of blood was then removed and mixed with 5 c.c. of 10 per cent. sodium citrate solution and reinjected into the jugular vein of the same dog. Blood taken at intervals of three minutes showed a gradually diminishing clotting time, until after one half hour the clotting time was found to be reduced to ten seconds. This experiment was later confirmed by Hedon.[5]

Subsequent experiments demonstrated that this action was due to the sodium citrate and not to the transfused blood. Weil [2] was the first to report this fact. He injected as much as 5 gm. intravenously in a human being and found that the coagulation time of the blood was

* From the Pathological and Medical Departments, Mount Sinai Hospital, New York. The work was done during the tenure of a George Blumenthal, Jr., Fellowship in Pathology.

1. Lewisohn, R.: Med. Rec. **87**:141, 1915.
2. Weil, Richard: Sodium Citrate in the Transfusion of Blood, J. A. M. A. **64**:425 (Jan. 30) 1915.
3. Hustin, A.: An. et bull. Soc. roy. d. sc. méd. et nat. de Bruxelles **72**:104, 1914.
4. Agote, L.: An. d. Inst. mod. de clin. med., Buenos Aires **1**:25, 1915.
5. Hedon, E.: Presse méd. **26**:57 (Feb. 4) 1918.

reduced by one-half about ten minutes after the injection. These observations have recently been amply confirmed by Neuhof and Hirschfeld [6] in a large series of surgical cases, using even larger doses than Weil (up to 9 gm.). They recommend the employment of sodium citrate in cases of hemorrhage and when a relatively bloodless operation is desired.

During the last four years, we have repeatedly employed this means of arresting secondary hemorrhages in a variety of medical conditions such as gastric ulcer, pulmonary tuberculosis, cerebral hemorrhage, typhoid fever and excessive bleeding from a tooth socket following extraction, and after tonsillectomy. From 3 to 6 c.c. of a 30 per cent. solution of sodium citrate (3 to 6 gm.) has usually been administered, very slowly, the intravenous injection taking from ten to fifteen minutes for completion.

We have not been able to convince ourselves that the intramuscular administration recommended by Neuhof and Hirschfeld [7] is by any means as efficacious. Leone [8] did not find any diminution of blood coagulation after intravenous injection of sodium citrate. But he used toxic doses. We have limited ourselves to its intravenous use in spite of the fact that its employment is not entirely without danger. In one case,[6] not in our hands, it has been followed by a fatality, undoubtedly due to a too hasty administration. If properly administered, from 3 to 6 gm. can be safely given to an adult of average size. In blood diseases, for reasons subsequently to be developed in this paper, its employment is at all times contraindicated.

This striking phenomenon, shortening the coagulation time of the blood, the exact opposite of what occurs in vitro, was made the subject of a detailed experimental study in order to ascertain what changes were induced by sodium citrate in the complicated mechanism of blood coagulation. For this purpose, the effect on each factor involved in coagulation was studied individually.

MATERIAL AND TECHNIC

Chemically pure sodium citrate was used for the solutions. Although the effect on dogs is probably more pronounced, cats were selected as the animals of choice in the laboratory, because they were more easily obtainable. Blood was withdrawn from various vessels (carotids, jugulars and femorals), preferably with an all-glass syringe or a cannula, before and after the intravenous injection of sodium citrate. The syringes were sterilized and washed with saline solution before use. Usually, 1.5 c.c. of blood was removed for each observation and divided

6. Neuhof, H., and Hirschfeld, S.: New York M. J. **95**:113, 1915.
7. Neuhof, H., and Hirschfeld, S.: Ann. Surg. **76**:1 (July) 1922.
8. Leone, G.: Riforma med. **38**:313 (April 3) 1922.

in two small test tubes. For the purpose of determining the coagulation time, half of the sample was put into a small test tube previously washed with saline solution (Lee and White [9]), and the rest of the blood was put into a second small test tube containing 0.03 c.c. of a 30 per cent. solution of sodium citrate. The second tube was immediately shaken in order to mix the blood and sodium citrate, and it was then allowed to stand about one half hour or longer to insure the sedimentation of the red blood cells so that the blood platelets could be easily counted in the supernatant plasma.

The citrate solution was injected very slowly because otherwise death from cardiac or respiratory failure rapidly ensued.[10] In a favorable experiment, the shortening of coagulation time begins within ten minutes and reaches its maximum within one hour.

Calcium.—Sodium citrate exerts its anticoagulant effect in vitro by a change in the calcium balance of the blood as shown by Sabbatani.[11] It might therefore be anticipated that the opposite effect which it exerts in vivo is also caused by a variation in the blood calcium. However, two sets of observations immediately contradict this possibility. First, we have been unable to find any change in the calcium content of the blood after intravenous administration of sodium citrate. The analyses were performed by Dr. J. S. Kohn, and are in agreement with the old observations of Sabbatani.[10] Secondly, the calcium in normal blood appears to be the optimum amount needed for coagulation (Clowes [12]). The addition of variable quantities of calcium chlorid to normal blood influences the rate of coagulation either very little or not at all.

Sodium citrate forms a loose compound with the inorganic calcium and does not remain in the blood stream long enough to be a factor (Salant).[13] Vines [14] has shown that it is the organic combined calcium that is of importance in blood coagulation. We could therefore eliminate calcium as the responsible factor in the hastening of blood coagulation after the intravenous injection of sodium citrate.

Fibrinogen.—The fibrinogen content of human and of cat's blood before and after citrate administration was determined according to

9. Lee, R. I., and White, P. D.: Am. J. M. Sc. **145**:495, 1913.

10. When sufficient sodium citrate was injected to induce death of the animal, the blood within the heart and great vessels was found to be incoagulable. When we recalcified this blood it coagulated promptly, an indication that death was due to calcium deprivation and not to any anaphylaxis-like phenomenon. When a large toxic dose was injected, the blood also became incoagulable but clotted on recalcification. The effect was due to the sodium citrate present in the blood stream, producing the same effect as in the test tube. This has also been noted by L. Sabbatani (Atti. d. r. Accad. d. sc. di Torino **36**:1, 27, 1901).

11. Sabbatani, L.: Compt. rend. Soc. de Biol. **54**:716, 1902.

12. Clowes, G. H.: J. Physical Chem. **20**:407, 1916.

13. Salant, W., and Wise, L. E.: Jour. Biol. Chem. **28**:27 (Dec.) 1916.

14. Vines, H. W. C.: J. Physiol. **55**:86 (May) 1921.

Gram's [15] method and also the most recently suggested method of Foster and Whipple.[16] No appreciable difference in the content of fibrinogen was observed after the injection, even when the coagulating time of the blood had been shortened to less than half. An increase in the amount of fibrinogen was thereby eliminated as the responsible factor.

Antithrombin.—The so-called antithrombin factor described by Howell as often responsible for variations in the relative coagulability of blood was also eliminated from consideration. We carried out observations in accordance with Howell's [17] and Hess's [18] recommendations and could find no change in this theoretical factor after the citrate had been injected.

Cytozyme and Serozyme (Thromboplastic Substance and Prothrombin).—Howell's [17] method of demonstrating the relative amount of prothrombin (or serozyme) was also employed. This theoretical precursor of thrombin (according to Howell) is studied by collecting the blood in sufficient potassium oxalate to prevent coagulation. The so-called prothrombin time is the coagulating time of the oxalated plasma after recalcification. We found that after injection of the sodium citrate, the prothrombin time was shortened, often in exact proportion to the diminution in the coagulation time of the whole blood.

Unfortunately, the results were not altogether constant. On investigation, this inconstancy was found to depend on the length of time that intervened between the drawing of the blood into the oxalate and its subsequent recalcification. If the oxalated blood was recalcified immediately after being drawn, the so-called prothrombin time was equivalent to the coagulation time of the unoxalated blood. If the oxalated blood was allowed to stand for ten or fifteen minutes before being recalcified, the prothrombin time was greatly reduced, perhaps from five minutes to one minute. We have therefore been unable to convince ourselves of the absolute accuracy of any of the quantitative observations on prothrombin. Citrated blood acts in similar and even more marked fashion than oxalated blood, so that the citrate method recommended by Gram [19] for blood coagulation cannot be considered reliable. However, when the specimens of oxalated or citrated blood drawn before and after the injection of sodium citrate were all recalcified at the same intervals after being drawn, the prothrombin time was found to be definitely shortened at the time after injection when the clotting time of the whole blood is

15. Gram, H. C.: Jour. Biol. Chem. **49**:279 (Dec.) 1921.
16. Foster, D. P., and Whipple, G. H.: Am. J. Physiol. **58**:365 (Jan.) 1922.
17. Howell, W. H.: Condition of the Blood in Hemophilia, Thrombosis and Purpura, Arch. Int. Med. **13**:76 (Jan.) 1914.
18. Hess, A. F.: J. Exper. Med. **21**:338, 1915.
19. Gram, H. C.: Bull. Johns Hopkins Hosp. **31**:364 (Oct.) 1920.

shortened. One can say, therefore, that during the period after injection when the clotting time is shortened, there is a marked increase in the activity of some thromboplastic substance in the plasma.

Blood Platelets.—In view of the fact that the chief source of the activating agent for blood coagulation is believed to be the blood platelets, careful counts of the platelets (in the plasma) were made before and at intervals after the administration of the sodium citrate.

The experiments were first checked up by a control experiment in which the procedure was the same except that the sodium citrate injection was omitted (Table 1).

It will be noted in Table 1 that the clotting times and blood platelet counts show only slight variations.

TABLE 1.—*Control Experiment*

Time	Coagulation Time	Blood Platelets
3:15	5 min.	352,000
3:25	6 min.	322,000
3:29	7 min.	313,000
3:34	7 min.	316,000
3:46	6 min.	352,000
3:55	6 min.	313,000
4:00	7 min.	345,800

TABLE 2.—*Effect of intravenous injection of 0.3 to 0.5 Gm. Sodium Citrate*

	Cat 3		Cat 4		Cat 11		Cat 12		Cat 13	
	Coagulation Time, Min.	Blood* Platelets	Coagulation Time, Min.	Blood* Platelets	Coagulation Time, Min.	Blood* Platelets	Coagulation Time, Min.	Blood* Platelets	Coagulation Time, Min.	Blood* Platelets
Before injection	8	620,800	11	1,139,200	11	569,600	14	640,000	8	429,000
5 minutes later	..	.....	..	.....	9	448,000	12	521,000	..	.....
10 minutes later	4	60,800†	3	1,560,000	6	512,000	3	96,000‡	8	256,000
20 minutes later	1½	270,000	2½	739,600	4	384,000	2	458,000	4½	384,000
40 minutes later	1½	510,000	2½	646,000	1½	368,000	3	325,000	2½	320,000
50 minutes later	..	.....	..	.....	..	.....	2	325,000	4½	387,000

* In plasma. † No clot retraction. ‡ Slight clot retraction.

When sodium citrate is injected intravenously, the blood platelets frequently show an immediate diminution, but their number more or less quickly returns to normal.

The experiments outlined in Table 2 illustrate this point.

An analysis of the experiments in Table 2 reveals that the intravenous injection of 0.5 gm. of sodium citrate in the cat results in the following changes:

1. A marked reduction in the coagulation time which begins within five minutes after the injection and reaches its maximum from one half

to one hour later. The maximum effect in Cat 11 represented a reduction in coagulation time from eleven minutes to one and one-half minutes.

2. A marked reduction in the number of blood platelets in the circulating blood. The most pronounced reduction was observed in Cat 3, in which the count was reduced from 620,800 to 60,800 within ten minutes after the injection. In some instances, the reduction is less marked and occurs more slowly. Within one-half hour, however, the count begins to rise toward normal.

3. When the blood platelet count reaches a very low point (as occurred ten minutes after injection in Cat 3 and fifteen minutes after in Cat 12), the clot resulting from the coagulation fails to retract. This confirms the accuracy of the low platelet counts.

4. The blood platelet counts would seem to indicate that between ten and fifteen minutes after the injection in Cats 3 and 12, more than 85 and 90 per cent. of the platelets had been suddenly destroyed or removed from the systemic circulation.

5. Although both a reduction in blood platelets and in the coagulating time of the blood is appreciable five minutes after the injection, the period of maximum reduction in platelets by no means corresponds to the period of maximum shortening in the coagulation time. In fact, the two curves never run parallel. The reduction in blood platelets reaches its maximum very rapidly and returns toward normal within a half hour as a rule; whereas the maximum shortening in the coagulating time of the blood occurs from one half to one hour after the injection (when the platelet count is often already back to normal), and may persist at this level for several hours and then only slowly return to normal within the succeeding twenty-four hours.

The impression gained, therefore, from these experiments is that the primary process is a destruction or removal of blood platelets from the circulating blood. If the platelets were reduced by a mere destruction within the circulating blood, the maximum shortening in the coagulating time would have occurred simultaneously with the maximum reduction in blood platelets. The platelets that had been in contact with the sodium citrate must therefore have been removed from the blood by some organ, perhaps the spleen or by the blood phagocytes and then gradually destroyed, thromboplastic substance (cytozyme) being thereby gradually liberated into the circulation. The spleen seems to us the more likely agent for the removal and destruction of platelets in view of the unquestioned rôle it plays in the similar mechanism involved in the so-called thrombocytopenic purpura (Kaznelson,[20] Brill and

20. Kaznelson, P.: Ztschr. f. klin. Med. **87**:133, 1919.

Rosenthal [21]). Furthermore, it is inconceivable that the blood phagocytes would be capable of removing a large number of the platelets from the circulating blood within a few minutes.

If our interpretation of the above described phenomena is true, the entire process already has its analogy in toluylendiamin poisoning. The difference between the action on blood of toluylendiamin and of sodium citrate is chiefly a difference in point of attack, the former affecting red blood cells, the latter the blood platelets. Toluylendiamin according to Joannovics and Pick [22] does not destroy red blood cells in vitro, but it does something to them because red cells which have been in contact with the chemical are rapidly removed from the circulation by the spleen and there destroyed. Similarly, sodium citrate does not destroy platelets in vitro: it preserves them in the test tube. In fact, this preservative action is employed as the basis for the use of sodium citrate in the present methods of counting blood platelets. After being in contact with sodium citrate, the platelets are suddenly and rapidly removed from the circulation, probably by the spleen, and then destroyed. The destruction of red cells after toluylendiamin poisoning is followed by the flooding of the body with the contents of the red cells, the blood pigments, with the resultant development of jaundice. The destruction of the blood platelets is followed by a discharge into the blood of their contents, the thromboplastic substance cytozyme, with the resultant shortening of the coagulation time of the blood.

This gradual destruction of blood platelets after their removal from the blood will account for the fact that the amount of cytozyme in the blood (as indicated by the coagulability) is often still increasing long after the blood platelet count has returned to within normal limits.

Mobilization of Blood Platelets.—The ease and rapidity with which the body can restore the total number of blood platelets after a large number have been removed from the circulation is, we believe, an important observation. The body is apparently able to mobilize large numbers of fresh platelets within a few minutes. In a few instances in humans and cats in which we have seen only relatively slight changes in the platelet count, this mobilization of fresh platelets may have occurred simultaneously with the withdrawal of the damaged platelets from the circulation, and so have partly masked any reduction in the number.

Such a mobile mechanism is needed as one of our most important defensive measures; for the arresting of hemorrhage and the primary formation of thrombi in the living body are produced by the agglutina-

21. Brill, N. E., and Rosenthal, N.: Am. J. M. Sc. **166**:503 (Oct.) 1923.

22. Joannovics, G., and Pick, E. P.: Ztschr. f. Exper. Path. u. Therap. **7**:185, 1909.

tion of blood platelets. The better known coagulation phenomena usually play only a secondary rôle, at least so long as the circulation is uninterrupted.

FURTHER TESTS OF THE THEORY

The above described theory, although it accounts for all the phenomena observed after the intravenous injection of sodium citrate and satisfactorily explains the shortening in the coagulation time, was subjected to two other series of experiments. If our explanation was correct, we felt that it would be important to study the effect of sodium citrate on animals that normally do not possess any blood platelets comparable to the mammalian, and also on human beings in whom, because of disease, there existed a marked numerical deficiency or disease of the platelets.

TABLE 3.—*Coagulation Time of Blood After Intravenous Injection of Sodium Citrate*

	Duck 1	Duck 2
Before citrate administration	5 min.	1 hour
		1 hour, 10 min.
Amount injected	0.5 gm.	0.25 gm.
5 minutes later	25 min.	1 hour
7½ minutes later	20 min.	
20 minutes later	24 min.	1 hour, 20 min.
40 minutes later	14 min.	
48 minutes later	0.25 gm. sod. citrate intraven.	
54 minutes later	11 min.	
1 hour, 5 minutes later	27 min.	
1 hour, 20 minutes later	16 min.	

Observations on Ducks.—Ducks are known to have no blood platelets. At least, the thrombocytes or homologues of the mammalian platelets are few in number.

Two ducks were used for the investigation. The wing vessels served well for the removal of the blood and for the injection of the citrate. One duck was injected with 0.25 gm., the other with 0.5 gm.

As can be judged from Table 3, the intravenous injection of sodium citrate in ducks either exhibits no effect on the coagulating time, or else produces a distinct prolongation. No period of shortening of coagulation time is demonstrable—a distinct contrast to the effect observed in animals that possess well developed platelets (cat, dog and human being).

Deleterious Effect of Sodium Citrate in Hemorrhagic Diseases.—The various hemorrhagic diseases are for the most part characterized by either a marked numerical or a qualitative deficiency in the blood platelets. It was therefore thought to be important to ascertain the effect of sodium citrate in these conditions. It was administered intravenously in two cases, each representing a separate clinical type of primary hemorrhagic blood disease; (1) essential thrombopenic purpura (the

so-called purpura hemorrhagica), which is characterized by a pronounced diminution in the number of blood platelets; (2) congenital hemophilia, in which the number of blood platelets is normal but in which the coagulation time of the blood is prolonged, possibly because of some qualitative deficiency in the platelets.

REPORT OF CASES

CASE 1.—*Essential Thrombopenia (Purpura Hemorrhagica).* This patient had a generalized purpuric skin eruption and was bleeding from the gums and nose. The blood examination revealed: hemoglobin, 90 per cent.; red cells, 4,864,000; white cells, 8,200; blood platelets, 300 (counted in undiluted plasma); differential count: polymorphonuclear neutrophils, 54.0 per cent.; eosinophils, 3.0 per cent.; basophils, 0.5 per cent.; myelocytes, neutrophilic, 0.5 per cent.; lymphocytes, 31.5 per cent.; monocytes, 4.5 per cent. The coagulation time was eight minutes; bleeding time (ear), twenty-five minutes. In the capillary resistance test (Hess [23]) numerous petechiae appeared within five minutes. There was no retraction of the blood clot for eight hours.

The remarkably low blood platelet count, the normal coagulation time contrasted with the prolonged bleeding time, the positive capillary resistance test and nonretraction of the blood clot showed that the case was a true purpura (essential thrombocytopenia).

TABLE 4.—*Findings in Case 2*

	Coagulation Time	Blood Platelets
Before sodium citrate injection	45 min.	192,000
15 minutes after	15 min.	280,000
2 hours, 20 minutes after	46 min.	170,000
3½ hours after	25 min.	130,000
24 hours after	1 hr., 25 min.	140,000
48 hours after	3 hrs. (soft clot)	110,000
72 hours after	25 min.	260,000

Six days after admission, the patient received a slow intravenous injection of 4.5 gm. of sodium citrate. The bleeding from the gums became worse the next day. The coagulation time of the blood increased gradually after the injection. The clotting time of the blood immediately before the injection of citrate was four minutes.

The citrate was injected slowly for twelve minutes, when it was stopped on account of the patient's complaining. Two minutes after sodium citrate injection the coagulation time was four minutes; eighteen minutes after, ten minutes; one hour and thirty minutes after, sixteen minutes; eighteen hours after, seventeen minutes.

The prolongation of the clotting time is interesting in view of the similar effect described above in animals which have few or no blood platelets. Blood platelet counts were also made at the same time that the tests for blood coagulation were performed. The platelets were counted in the undilated citrated plasma.

Before the citrate injection, the platelets numbered 400 per cubic millimeter; two minutes after injection, they numbered 400; eighteen minutes after 300; one hour and thirty minutes after 200; eighteen hours after 150. The reduction in the number of blood platelets following the injection of sodium citrate runs parallel with the increased coagulation time.

CASE 2.—*Congenital Hemophilia.* One observation on this disease has already been published by Ottenberg.[24] In 1916, he injected 0.6 gm. of sodium citrate

23. Hess, A. F.: Hemophilia, Arch. Int. Med. **17**:203 (Feb.) 1916.
24. Ottenberg, R.: Proc. Soc. Exper. Biol. & Med. **13**:1011, 1916.

intravenously in a patient suffering from congenital hemophilia and observed that the coagulation time of the blood was shortened from ninety-five to twenty-five minutes. Forty-eight hours later, the coagulation time was prolonged to two hours and twenty-five minutes.

Our own observations confirm this finding. We injected 3.0 gm. of sodium citrate in a hemophilic patient who has been repeatedly admitted to the hospital for bleeding from the gums or hemarthroses. The result is summarized in Table 4.

Sodium citrate produces in hemophiliacs early shortening in coagulation time exactly as it does in normal individuals, but this shortening is purely transitory and is followed twenty-four and forty-eight hours later by a pronounced prolongation in coagulation time and by an increase in the bleeding tendency. The explanation for this deviation from the normal result is not obvious. It is possibly dependent on an accentuation of the qualitative deficiency in the blood platelets. In addition, the prolongation of coagulation time twenty-four and forty-eight hours after the injection was associated with a pronounced reduction in the number of blood platelets.

Our experience with sodium citrate in the hemorrhagic diseases is sufficient to indicate that it is not only an ineffective remedy, but actually a dangerous one in these conditions. Instead of producing a shortening of the coagulation time of the blood as in normal individuals, it produces a pronounced delay in coagulation. In those conditions characterized by a marked numerical deficiency in blood platelets (purpura hemorrhagica), it may result in almost complete disappearance of platelets from the circulating blood and a definite increase in the bleeding tendency.

SUMMARY

Sodium citrate, when administered intravenously in large doses (0.5 gm. for dog or cat, from 3.0 to 8.0 gm. for man), produces a pronounced and progressive shortening in coagulation time of the blood, which usually reaches it maximum within one hour and may persist for many hours. As a rule, the coagulation time slowly returns to normal within twenty-four hours.

This action of sodium citrate on the coagulation of the blood in vivo is exactly opposite to that occuring in vitro. We believe that it is dependent on some effect on the blood platelets, which are not directly destroyed by the citrate but are damaged by contact with it and are then removed from the circulation by the spleen or other organs, where they are destroyed and their thromboplastic contents gradually liberated into the circulating blood. This theory is based on the following observations:

1. In the test tube, sodium citrate does not destroy the platelets, but it affects them so that they are actually preserved and are therefore more easily counted.

2. Within a few minutes after the intravenous injection of sodium citrate, the blood platelets often begin to diminish in number, the maximum reduction being usually observed after from ten to fifteen minutes and the number as a rule returning to normal after from one half to one hour. The greatest reduction in blood platelets was observed in cats, in two of which 85 and 90 per cent. of the platelets disappeared from the circulating blood within ten and fifteen minutes, respectively, and the count again reached normal a half hour after the injection.

3. Increasing amounts of free thromboplastic substance (cytozyme probably derived from platelets, begin to appear in the blood stream as the coagulation time is shortened.

4. No changes in the content of the blood as to the other factors concerned in coagulation, such as calcium, fibrinogen or antithrombin, are demonstrable.

5. The increase in the thromboplastic agent cytozyme and the shortening in coagulation time of the blood do not occur simultaneously with the numerical change in the platelets, but follow it. The maximum shortening in coagulation time occurs some time after the numbers of platelets have again returned to normal, and persists for hours.

6. The characteristic shortening of coagulation time after intravenous injection of sodium citrate does not occur in animals (ducks) in whose blood few or no platelets occur. If sufficient citrate is administered, the opposite effect is produced in such animals and the coagulation time may be markedly prolonged.

7. The shortening of coagulation time after intravenous injection of sodium citrate likewise fails to occur in human beings suffering from hemorrhagic blood diseases that are characterized by a pronounced numerical deficiency in blood platelets. In purpura hemorrhagic, in which such a reduction in the number of platelets is regularly present, the injection of sodium citrate may be followed by almost complete disappearance of platelets from the circulating blood and a prolongation of the clotting time.

In congenital hemophilia, in which there is presumed to be some deficiency in the quality of blood platelets, the injection of sodium citrate is followed by a prolongation in the coagulation time, a diminution of the blood platelets and a marked increase in the bleeding tendency.

Sufficient evidence has been presented, therefore, to indicate that the shortening of coagulation time after injection of sodium citrate in normal individuals or animals is due to some influence on the blood platelets.

That this is not a direct destruction is proved by the test tube experiment and by the fact that the maximum shortening of coagulation times does not occur simultaneously with the maximum reduction in platelets, but follows from ten minutes to one hour later. This sequence suggests that the platelets after contact with the citrate are damaged and removed from the circulation by some organ, there destroyed, and their thromboplastic contents gradually liberated into the blood stream. The removal or modification of damaged or altered blood platelets is probably one of the functions of the spleen, especially in view of the rôle that it is presumed to play in chronic thrombocytopenia or purpura hemorrhagica.

With these observations as a basis, the slow intravenous injection of large doses of sodium citrate up to 5 gm. has been successfully employed in arresting hemorrhages due to gastric ulcer, typhoid fever, pulmonary tuberculosis and other bleeding conditions that are not accompanied by diminution or disease of the blood platelets.

Although the coagulation time of the blood is often materially shortened, no tendency to intravascular thrombosis has ever been observed, and we believe that this possibility can be dismissed as an unlikely danger. The real danger to be guarded against is a too hasty injection. The citrate should be well diluted and the procedure should take at least fifteen minutes continuously, not intermittently, during that period, to avoid too great a concentration in the heart's blood at any one time. For the sake of absolute safety, and because of other manifest advantages, we would advise its administration in from 200 to 500 c.c. of blood in the form of the citrate transfusion of Lewisohn.

In hemorrhagic blood diseases, for reasons detailed above, its use is strictly contraindicated.

NARCOTIC DRUG ADDICTION

II. THE PRESENCE OF TOXIC SUBSTANCES IN THE BLOOD SERUM IN MORPHIN HABITUATION *

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In our first paper in this series on narcotic drug addiction,[1] we dealt with the question whether the continuous taking of morphin causes the presence in the blood serum of any substance which has a protective effect against morphin, and arrived at negative conclusions.

Another question is whether any specific toxic substance is produced by morphin habituation. This question, which is closely related to the first, has a more direct practical bearing on the current theories of the nature of morphin addiction and the causation of withdrawal symptoms, and also on treatment. There has been considerable controversy on this subject, and a more or less widespread belief that there is such a substance and that it is the cause of the well known symptoms of morphin withdrawal when no longer neutralized by the continued administration of morphin; and some methods of treatment of drug addiction have been founded upon this belief.

The scientific basis for this conception originally rested upon the work of Marmé,[2] who reported the finding of oxydimorphin in the feces, lungs and liver of dogs habituated to morphin. He further stated that oxydimorphin produced symptoms similar to those of morphin withdrawal, when injected into nontolerant dogs. Marmé's results have been disproved by numerous subsequent investigators.[3]

The belief is at present based solely upon the work of Valenti,[4] who, in 1914, reported a series of experiments in which he investigated the effects produced on the circulation of normal dogs by the intravenous injection of serum of the blood of dogs accustomed to increasing doses of morphin, and which were in withdrawal when the blood was

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1. Pellini, E. J., and Greenfield, A. D.: Arch. Int. Med. **23**:279 (Sept.) 1920.
2. Marmé: Deutsch. med. Wchnschr. **14**:197, 1883.
3. A review of this work is contained in an article by Du Mez, A. G.: Increased Tolerance and Withdrawal Phenomena in Chronic Morphinism, J. A. M. A. **72**:1069 (April 12) 1919.
4. Valenti: Arch. f. exper. Path. u. Pharmakol. **75**:437, 1914.

obtained. Since his results have never been tested by other investigators, we have made the study of this question the subject of the present paper.

446 XXII. Adriano Valenti.

Versuch 6.

Hund von 9 kg, Tracheotomie, linke Carotis, rechte Jugularis externa. Das diesem Tier injizierte Serum stammte von einem Hund von 11 kg; dieser war 55 Tage lang mit Morphium behandelt worden, beginnend mit 0,1 g und langsam ansteigend bis zu einer Tagesmenge von 3,15 g Morphium hydrochloricum subkutan, wobei es im ganzen 69,95 g erhielt. Der Aderlaß an der Vena femoralis wurde am dritten Tage der Abstinenz ausgeführt, und 190 ccm Blut aufgefangen, das zentrifugiert 80 ccm zitronengelbes Serum ergibt.

Zeit Uhr	Höchste und niedrigste Pulsfrequenz in einer halben Minute	Höchster und niedrigster Blutdruck in Millimeter Quecksilber	Bemerkungen
9,34	66	160—164	Normal
9,44	60	158—162	»
9,51	60	154—162	»
9,58	—	—	Es wird mit der Seruminjektion begonnen
10,3	54—60	170—178	Nach 5 ccm
10,6	66—72	154—162	» 8 »
10,9	72—78	152—162	» 11 »
10,15	72—108	150—164	» 17 »
10,18	72—106	140—164	» 20 »
10,20	66—90	150—164	» 22 »
10,24	72—108	140—160	» 26 »
10,25	66—68	164—174	» 27 »
10,26	—	—	Die Injektion wird unterbrochen
10,30	78—78	154—162	
10,33	72—90	144—162	
10,34	—	—	Die Injektion wird fortgesetzt
10,40	72—78	150—162	Nach 33 ccm
10,43	72—84	142—160	» 36 »
10,48	66—96	132—154	» 40 »
10,51	60—72	140—154	Die Injektion wird sistiert
10,55	78—90	140—152	
10,59	66—72	140—152	
11,10	74	152—156	

Fig. 1.—Reproduction of a page of Valenti's article containing a protocol of an experiment giving figures of normal pulse rate and blood pressure and variations following the injection of serum from a dog in the withdrawal stage.

Valenti's first work consisted in injecting into normal dogs the blood serum from dogs which he had addicted to morphin, and from which the morphin had been withdrawn for a period of three days at the time

of obtaining the blood. A typical experiment is most easily shown by reproducing one of his protocols (Figs. 1 and 2). He found certain circulatory disturbances, namely arrhythmia and marked increase in

Experimentelle Untersuchungen üb. d. chronischen Morphinismus usw. 447

Tabelle 6.

		Vor der Injektion	Nach der Injektion
Blutdruck in Millimeter Quecksilber	höchster	164	178
	niedrigster	154	152
		10 mm	26 mm
Pulsfrequenz in einer halben Minute	höchste	66	108
	niedrigste	60	60
		No. 6	No. 48

Es zeigt sich also sehr deutlich, daß, obgleich geringere Serummengen als bei den anderen Tieren injiziert wurden, diese imstande sind, größere Schwankungen des Blutdruckes und des Pulses hervorzurufen; vor allem aber erscheint bei diesem Versuch das Phänomen der Schwankungen im Herzrhythmus im gleichen Zeitabschnitt sehr auffällig. In der zweiten hier angeschlossenen Kurve sind wenigstens drei verschiedene Pulsrhythmen zu bemerken, und diese Arhythmien hielten den ganzen Versuch hindurch an, was aus den kurzen hier angeführten Kurven besser als aus den Zahlen zu ersehen ist.

Versuch 7.

Hündin von 6,4 kg, Tracheotomie, linke Carotis, rechte Jugularis externa. Das diesem Tier injizierte Serum stammt aus dem Blut eines Hundes von 9,6 kg, der in 48 Tagen bei einer Anfangstagesdosis von 0,02 bis zu

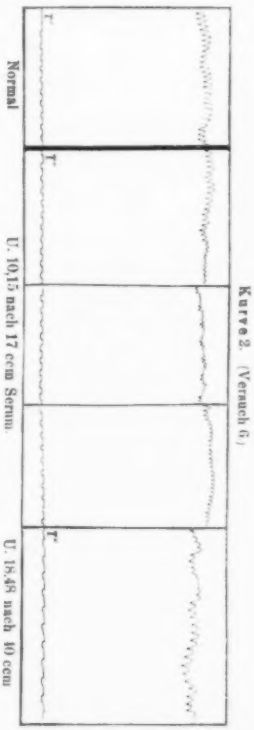

Fig. 2.—Continuation of Figure 1 giving a table showing maximum variations in pulse rate and blood pressure before and after serum injection and a tracing of carotid blood pressure from which these figures are obtained.

variability of the heart rate and blood pressure. Control experiments, using serum from the blood of normal dogs, showed but slight deviations.

He next undertook to determine whether there is any relation between the total amount of morphin administered to the addicted dogs and the degree of circulatory disturbances produced by their serum. He concludes that more pronounced effects are produced by the serum of the dogs receiving the largest total amount of morphin during the period of addiction.

He then investigated the question whether the intensity of the effects produced by the serum was in direct relation to the length of the period of withdrawal. He injected serum of blood drawn from dogs from which the morphin had been withdrawn for periods of thirty-six hours, ten days and twenty days, respectively. Under similar conditions as to total amount of morphin administered, the period of withdrawal appeared to have no relation to the intensity of the circulatory effects produced by the serum.

His concluding experiments were to determine whether circulatory disturbances similar to those produced by injecting the serum of addicted dogs into normal dogs could be found in the addicted dogs themselves during the period of withdrawal. He took the blood pressure and heart rate of dogs before addiction and at thirty-six hours, three days and twenty-one days, respectively, after withdrawal. He reports the same type of circulatory disturbances in these animals as in the normal dogs injected with serum of addicted dogs. During observation of the blood pressure and heart rate, he administered by subcutaneous injection increasing doses of morphin solution until the dose which the animals had received on the last day of their morphinization period had been passed. The disturbances became gradually weaker, and finally disappeared as soon as the previously accustomed dose was reached. A dose slightly over this produced the definite "morphin pulse," as in a dog not accustomed to morphin.

EXPERIMENTAL WORK

Our work consisted of duplication of the most significant feature of Valenti's work and of additional tests of our own. The latter comprised electrocardiographic studies; injection of serum into cats with a view to observing any effects on behavior or general symptoms, and studies of the chemistry of the blood of habituated dogs.

In duplicating Valenti's work, the first question that suggested itself was the form of anesthesia to be used. Valenti fails to state what anesthetic he used; in fact, he does not specifically state that he used any. As he subjected the normal dogs into which the serum was injected to tracheotomy, and specifies only in the cases of the morphinized dogs, on which he made direct observations, that the experiments were performed without tracheotomy and without narcosis, it

is fair to assume that in all the serum injection experiments he used ether by inhalation. We therefore made preliminary tests with ether administered in the customary way. With this method, we were unable to maintain a sufficiently uniform light anesthesia, even when the ether was given through a cannula in the trachea, to prevent the occurrence of circulatory variations due to variability in the degree of anesthesia.

We then attempted to use fixed anesthetics such as chloretone, but found that the dose required to maintain continued, uniform anesthesia produced too great circulatory depression, making the circulation not sufficiently sensitive to possible slight effects of the fluid injected. We were thus brought to the necessity of adopting some method by which anesthesia could be maintained indefinitely at a uniform degree while the circulation was allowed to retain its normal lability.

At this stage of our work we came in contact with Dr. Ben Morgan, who had recently perfected a new apparatus for the uniform administration of ether, embodying the principles of rebreathing and positive pressure, and permitting exact control of the amount of ether administered.[5] We were fortunate in obtaining the personal assistance of Dr. Morgan in administering ether for us by his method.

Our method of obtaining the serum for injection was as follows: A male dog of 17.5 kg. was habituated to morphin throughout a period of ten months. At the start, 10 mg. of morphin hydrochlorid per day was administered subcutaneously, and the dose was gradually increased to 2.75 gm. a day, which was given daily during the last month of the period. During the ten months, the animal lost 3 kg., but showed no other evidences of malnutrition. The total amount of morphin hydrochlorid administered throughout the period was 168.62 gm.

The question had arisen in our minds as to the point of time, after stoppage of morphin administration, at which the blood should be withdrawn to obtain the serum for injection. We noted that Valenti experimented with serum of blood obtained at various stages of withdrawal, and reports that no difference in effects is observed when the blood is drawn at any time from thirty-six hours to twenty days. It occurred to us that if there is any toxic substance in the blood of a morphin habituated dog, such substance should be present in maximum amount or strength at the time of greatest intensity of the withdrawal symptoms. It therefore seemed advisable to ascertain this time before proceeding further. As we had been unable to observe any gross symptoms at any time after the withdrawal of the morphin which would indicate a stage of maximum intensity, and since our work was directed especially toward circulatory changes, we made electrocardiographic

5. Morgan, Ben: Modern Hosp. **5**:215, 1915.

studies of the heart rate of habituated dogs at various stages of withdrawal. This work was done on other dogs which we had habituated to morphin and showed that the heart rate rises after withdrawal to a maximum point, which is reached in about forty hours, and followed by a gradual decline, reaching normal during a period of from two to three weeks.

We drew the blood for this experiment forty-one and one-half hours after the dog had received the last dose of morphin. Electrocardiographic observations were made on this dog, the second one being made just before obtaining the blood. Table 1 shows the results.

Our technic was as follows: The blood was collected by means of a large gage hypodermic needle thrust through the skin and into the external jugular vein. It was allowed to flow into 50 c.c. centrifuge tubes and was immediately centrifuged and decanted. By this procedure, any possible effect of a local anesthetic was obviated. In order to avoid possible deterioration of the serum, it was used the same day.

TABLE 1.—*Effect of Morphin Withdrawal on Heart Rate*

Time After Withdrawal	Heart Rate per Min.
18 hours	134
41 hours	146
70½ hours	119
94 hours	119
115 hours	124
2 weeks	99
3 weeks	108

The normal dog used for the purpose of testing the effects of the above mentioned serum was a male dog weighing 10 kg. The ether was administered first through a mask, and when surgical anesthesia was obtained the left carotid artery, the left external jugular vein and the trachea were exposed, and a cannula inserted in each. The animal was then placed on its side, the tracheal cannula was connected to the ether apparatus, the artery to a mercury manometer and the vein to the buret containing the serum. The dog was kept warm by coverings and by an electric hot plate placed under the dog board. The buret containing the serum was water-jacketed and the serum maintained uniformly at body temperature.

On completion of the operative procedures, the administration of ether was regulated until the optimum depth of anesthesia was reached, as ascertained by the corneal reflex. This occurred about five minutes before the first normal record was taken, and the rate of ether administration remained constant from that time until the close of the experiment. Observations of the corneal reflex at frequent intervals during the progress of the experiment showed that the optimum depth of

anesthesia was preserved by this rate of administration. Table 2 shows the results obtained.

In some of his protocols, Valenti gives two readings, both of heart rate and blood pressure, for each point of time. Our own records were so lacking in sudden variations that there was no occasion for us to follow his method in this particular.

TABLE 2.—*Effect of Serum of Morphinized Dog in Withdrawal*

	Time	Heart Rate per Min.	Blood Pressure in Mm. Hg	Remarks
(a)	2:05	180	170	Before injection
	2:10	195	171	Before injection
	2:15	192	168	Before injection
(b)	2:20	195	166	Before injection
	....	...	...	Injection of serum started (rate 1 c.c. per min.)
	2:25	186	163	After 5 c.c. of serum
(c)	2:29	186	158	After 9 c.c. of serum
	2:32	187	164	After 12 c.c. of serum
	2:35	187	168	After 15 c.c. of serum
	2:38	192	166	After 18 c.c. of serum
	2:41	192	164	After 21 c.c. of serum
	2:44	195	162	After 24 c.c. of serum
(d)	2:47	198	158	After 27 c.c. of serum
	2:50	195	158	After 30 c.c. of serum
	2:53	195	166	After 33 c.c. of serum
	2:56	190	164	After 36 c.c. of serum
	2:59	190	164	After 39 c.c. of serum
	3:02	190	168	After 42 c.c. of serum
	3:05	186	164	After 45 c.c. of serum
(e)	3:08	192	172	After 48 c.c. of serum
	3:11	195	170	After 51 c.c. of serum
	3:14	195	162	After 54 c.c. of serum
	3:17	195	164	After 57 c.c. of serum
	3:20	195	166	After 60 c.c. of serum
	3:23	195	164	After 63 c.c. of serum
(f)	3:26	187	162	After 66 c.c. of serum
	....	...	..	Injection stopped
	3:29	195	162	
	3:32	196	158	
(g)	3:35	195	159	
	3:38	195	160	
	3:42	196	162	
(h)	3:45	196	162	

	Before Injection	After Injection
Blood Pressure in Mm. Hg		
Highest	171	172
Lowest	166	158
	5	14
Heart Rate per Min.		
Highest	195	196
Lowest	180	186
	15	12

We next took, for purposes of comparison, a similar record of a dog injected with normal dog serum, all other conditions being identical. The weight of the dog was 9 kg. Table 3 gives the results obtained.

Figure 4 consists of sections of the record chosen at points corresponding as nearly as possible to those given from the record of the preceding experiment.

Comparison of the records obtained with normal serum and serum of the morphinized dog in withdrawal shows no such effects of the latter as were described by Valenti, but in view of the disparity between our results and his, we felt that additional work along somewhat dif-

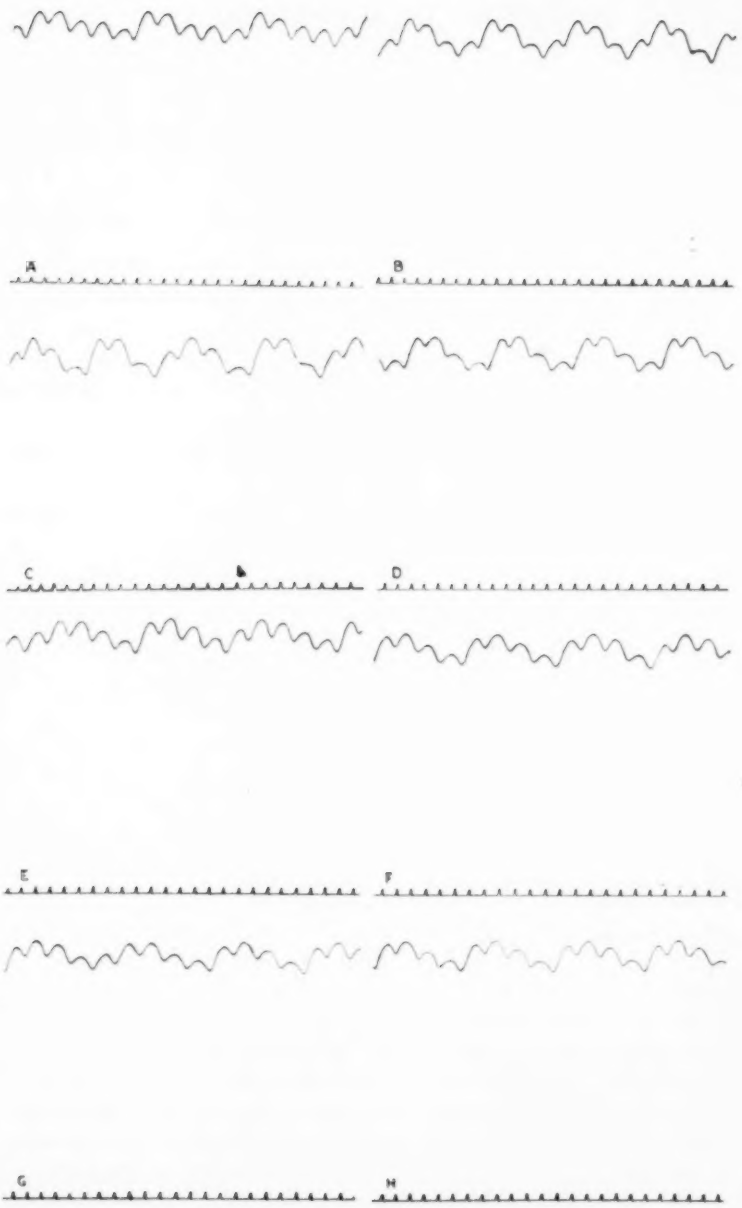

Fig. 3.—Sections of blood pressure records from the carotid artery taken at points marked with marginal letters in Table 2. The serum injected was from a dog in the stage of morphin withdrawal. A-B represent normal records. C-H represent the records after the injection. The record of the time marker indicates fifths of seconds and also serves as the zero base line for the blood pressure record.

ferent lines would be desirable, and next proceeded to electrocardiographic studies. By this procedure, we were enabled to dispense entirely with anesthesia and thus avoid any possible disturbing factor that might be due to the anesthetic. Moreover, it afforded a more sensitive means of testing the heart rate and rhythm.

In these studies, we exercised the greatest care. Our first step was a preliminary period of training of the dog, which was a female weigh-

TABLE 3.—*Effect of Normal Dog Serum*

	Time	Heart Rate per Min.	Blood Pressure in Mm. Hg	Remarks
(a)	4:06	160	118	Before injection
	4:10	168	120	Before injection
	4:15	162	117	Before injection
(b)	4:20	160	116	Before injection
	....	...	...	Injection of serum started
	4:23	156	116	After 3 c.c. of serum
	4:26	162	118	After 6 c.c. of serum
(c)	4:29	165	122	After 9 c.c. of serum
	4:31	168	124	After 12 c.c. of serum
	4:34	168	122	After 15 c.c. of serum
	4:37	168	123	After 18 c.c. of serum
	4:40	171	123	After 21 c.c. of serum
	4:43	171	121	After 24 c.c. of serum
(d)	4:46	174	119	After 27 c.c. of serum
	4:49	171	120	After 30 c.c. of serum
	4:51	174	122	After 33 c.c. of serum
	4:54	174	122	After 36 c.c. of serum
	4:57	174	118	After 39 c.c. of serum
	5:00	174	122	After 42 c.c. of serum
	5:03	174	120	After 45 c.c. of serum
(e)	5:06	177	122	After 48 c.c. of serum
	5:09	177	124	After 51 c.c. of serum
	5:12	177	124	After 54 c.c. of serum
	5:15	180	124	After 57 c.c. of serum
(f)	5:18	183	122	After 60 c.c. of serum
	....	...	...	Injection stopped
	5:23	183	119	
(g)	5:28	183	120	
	5:33	180	120	
(h)	5:38	177	126	

	Before Injection	After Injection
Blood Pressure in Mm. Hg		
Highest	120	126
Lowest	116	116
	4	10
Heart Rate per Min.		
Highest	168	183
Lowest	160	156
	8	27

ing 9 kg. This period covered three weeks. The training consisted in accustoming the dog to lie quietly on its side in a comfortable position in a room which was kept absolutely quiet, until it was able to maintain this position in perfect relaxation for about two hours at a time. The dog was kept warm by covering. After this stage of training had been reached, the electrodes and a respiration tambour were attached, and the dog was accustomed for a further period to these additional conditions. For several days before the actual experiments were started, slight skin incisions were made in the neck, simulating the exposing of the external jugular vein.

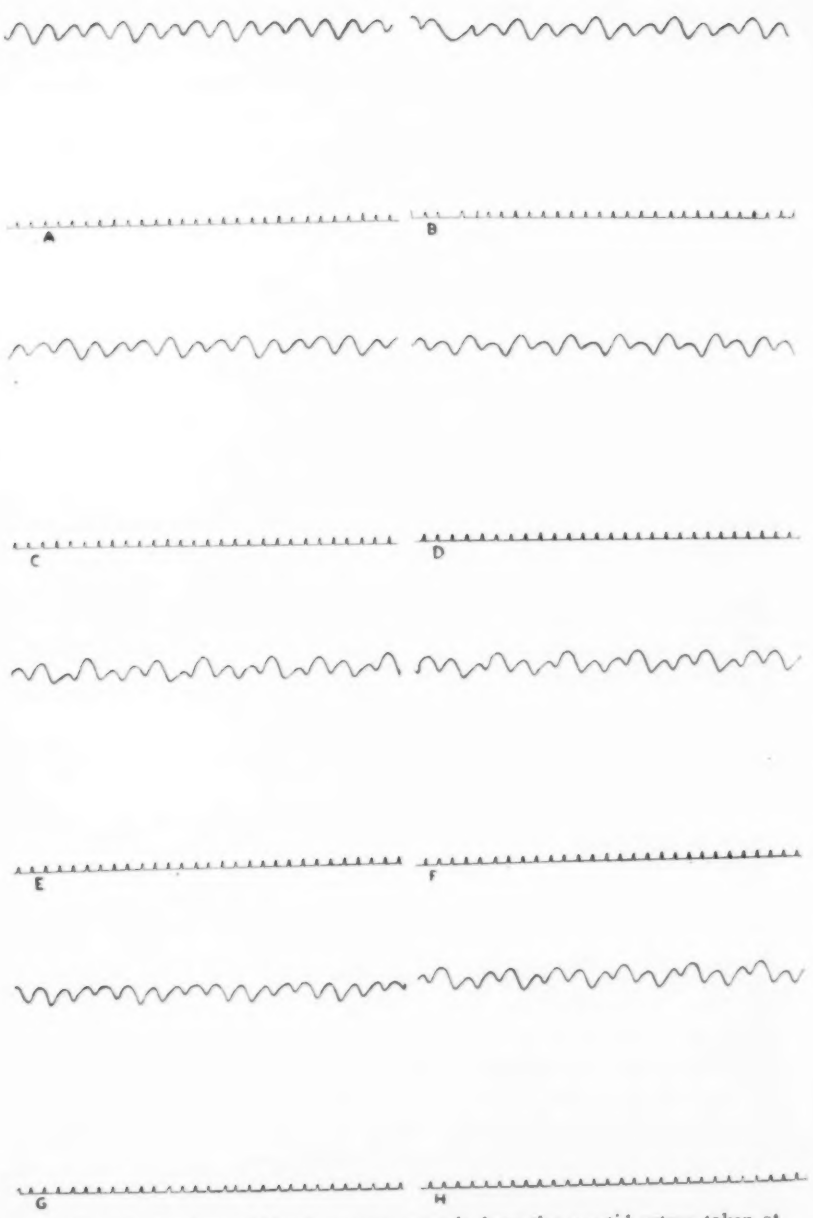

Fig. 4.—Sections of blood pressure records from the carotid artery taken at points marked with marginal letters in Table 3. The serum injected was normal dog serum. A-B records before injection. C-H records after injection.

In studying this dog, we took not only the electrocardiograms but also the respiratory tracings on the same film, synchronized as nearly as possible with the heart record. This was accomplished by attaching to the dog's chest a respiration tambour, connected by a rubber tubing to a recording tambour so placed that the lever moved across the aperture of the camera of the electrocardiographic apparatus. The latter was in a different room, some distance from that in which the dog was placed, to avoid disturbance by noise. In taking the electrocardiograms, we confined ourselves to the second lead throughout.

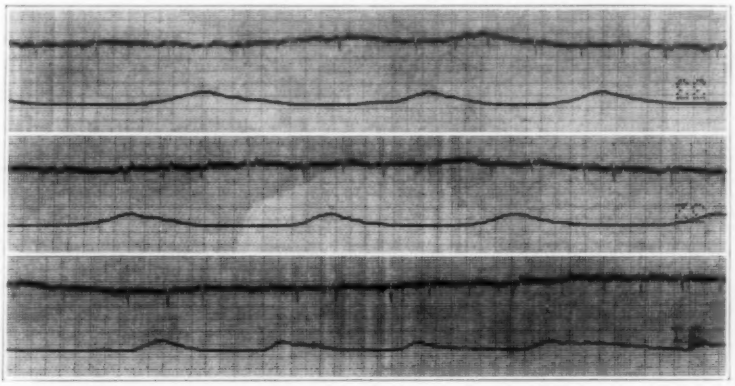

Fig. 5.—Sections of electrocardiograms (second lead) of a normal dog from which Table 4 was compiled. The upper tracing in each record represents the respiratory cycle.

Our first experiment with this dog consisted in taking electrocardiograms under the above described conditions, without injection, to obtain a normal record. Table 4 shows the results of three electrocardiograms taken at five-minute intervals.

TABLE 4.—*Electrocardiographic Studies of Normal Dog*

No. of Film	Heart Rate per Min.
31	102.5
32	97.7
33	90.3

In the accompanying electrocardiograms, it will be noted that the length of the individual complexes varies. On analysis, it appears that these variations occur regularly at definite intervals, and when compared with the tracing of the respiration it will be seen that there is a definite relationship between the rhythms of the respiration and the heart. It is clearly evident that the variation in heart rhythm is of

respiratory origin and must be discounted in estimating the effects of any injection. From our experience in electrocardiographic studies of other dogs, we have found that respiratory sinus arrhythmia is always present in the unanesthetized animal.

The next experiment on this dog, after an interval of five days, consisted in taking electrocardiograms with the injection of normal dog serum. The serum was kept warm during the injection, which was made into the external jugular vein, into which a cannula had been placed, without any evidence of pain or struggling on the part of the animal. Table 5 gives the results of this experiment.

TABLE 5.—*Electrocardiographic Study of Effect of Normal Dog Serum*

No. of Film	Time	Heart Rate per Min.	Remarks
41	2:55	122.4	Before injection
42	3:00	117.0	Before injection
43	3:05	127.2	Before injection
..	....	.....	Injection started
44	3:09	120.8	After 10 c.c. serum
45	3:13	123.9	After 20 c.c. serum
46	3:17	115.2	After 30 c.c. serum
47	3:21	127.8	After 40 c.c. serum
48	3:25	110.2	After 50 c.c. serum
..	....	.....	Injection stopped
49	3:30	139.6	
410	3:35	134.8	
411	3:45	138.3	

Heart Rate per Min.	Before Injection	After Injection
Highest	127.2	139.6
Lowest	117.0	110.2
	10.2	29.4

Our final experiment with this dog, performed four days later, consisted in injecting, in place of normal serum, serum obtained from the blood drawn from the morphinized dog in withdrawal cited above, other conditions being identical with those of the preceding experiment. Table 6 shows the results of this experiment.

TABLE 6.—*Electrocardiographic Study of Effect of Serum of Morphinized Dog in Withdrawal*

No. of Film	Time	Heart Rate per Min.	Remarks
51	4:40	102.3	Before injection
52	4:45	105.4	Before injection
53	4:50	80.0	Before injection
..	....	....	Started injection
54	4:54	96.0	After 10 c.c. serum
55	4:58	87.4	After 20 c.c. serum
56	5:02	81.0	After 30 c.c. serum
57	5:06	83.8	After 40 c.c. serum
58	5:10	85.8	After 50 c.c. serum
..	....	.....	Injection stopped
59	5:15	72.8	
510	5:20	75.6	
511	5:30	86.6	

Heart Rate per Min.	Before Injection	After Injection
Highest	105.4	96.0
Lowest	80.0	72.8
	25.4	23.2

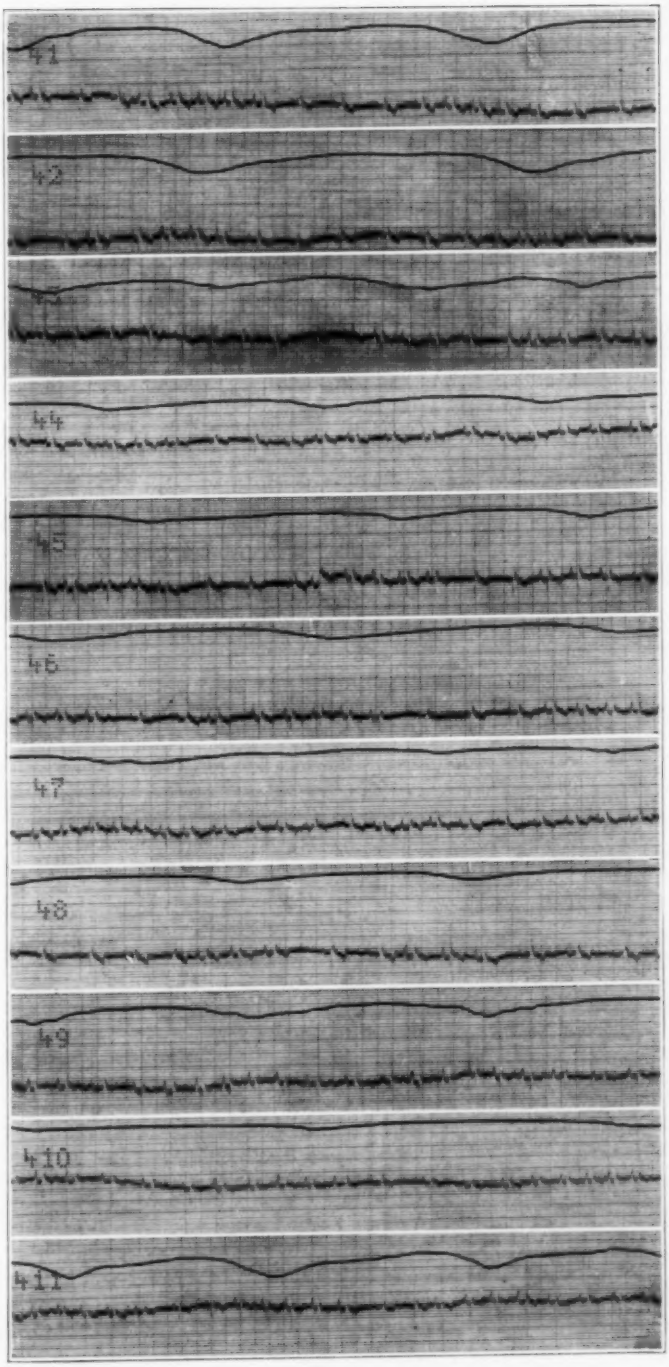

Fig. 6.—Sections of electrocardiograms (second lead), showing the effect of normal dog serum, from which Table 5 was made.

Comparison of these results with those of the preceding experiment shows no effects from the serum of the morphinized dog in withdrawal comparable to those shown by Valenti, thus confirming the results shown in Tables 2 and 3.

Besides studying changes in heart rate, the electrocardiograms were analyzed also for the maximum variations in the auricular complex, the ventricular complex, the complete cardiac diastole, the sequence and the rhythm of the heart. The results of the analysis did not show any effect that could be attributed to the serum of the morphinized dog in withdrawal and such variations as occurred were fully explained by respiratory sinus arrhythmia.

Since the foregoing experiments were confined to a study of possible effects on the circulation, we thought it desirable to extend the scope of our investigation to include other studies which might throw light on the effect of the serum, such as possible effects on the central

TABLE 7.—*Data Regarding Serums Used for Cat Experiments*

Experiment	Period of Addiction	Daily Dose of Morphin at Close of Period	Time of Drawing Blood After Withdrawal of Morphin
1	3 months	0.4 gm.	2 days
2	6 months	5.0 gm.	3 days
3	3 months	0.5 gm.	2 days
4	10 months	2.75 gm.	41½ hours
5	1 year	1.0 gm.	3 days
6	1 year	1.0 gm.	18 hours

nervous system or on the chemical composition of the blood. We therefore conducted, concurrently with our experiments on the circulation, two other series, in one of which we endeavored to ascertain by observation of the behavior and general symptoms of cats injected with such serum, whether any effects were produced, especially any referable to the central nervous system. Our technic in this series was as follows: The cats, which were not anesthetized, were placed in a box from which the head and neck alone projected; the external jugular vein was exposed just sufficiently to permit the insertion of a hypodermic needle, and 10 c.c. of serum was quickly injected by means of a syringe. The cat was then immediately released, the whole procedure described taking not more than three or four minutes. The animal was then kept under close observation for an hour or more, being allowed to roam at will in the laboratory. Six cats were injected with serum, and Table 7 gives data regarding the dog serum used in each case.

In all cases, the behavior of the cats was entirely normal, and they showed no effects from the injection of the serum.

Our final series consisted in analysis of the blood of morphinized dogs in withdrawal. The analysis of the blood was performed accord-

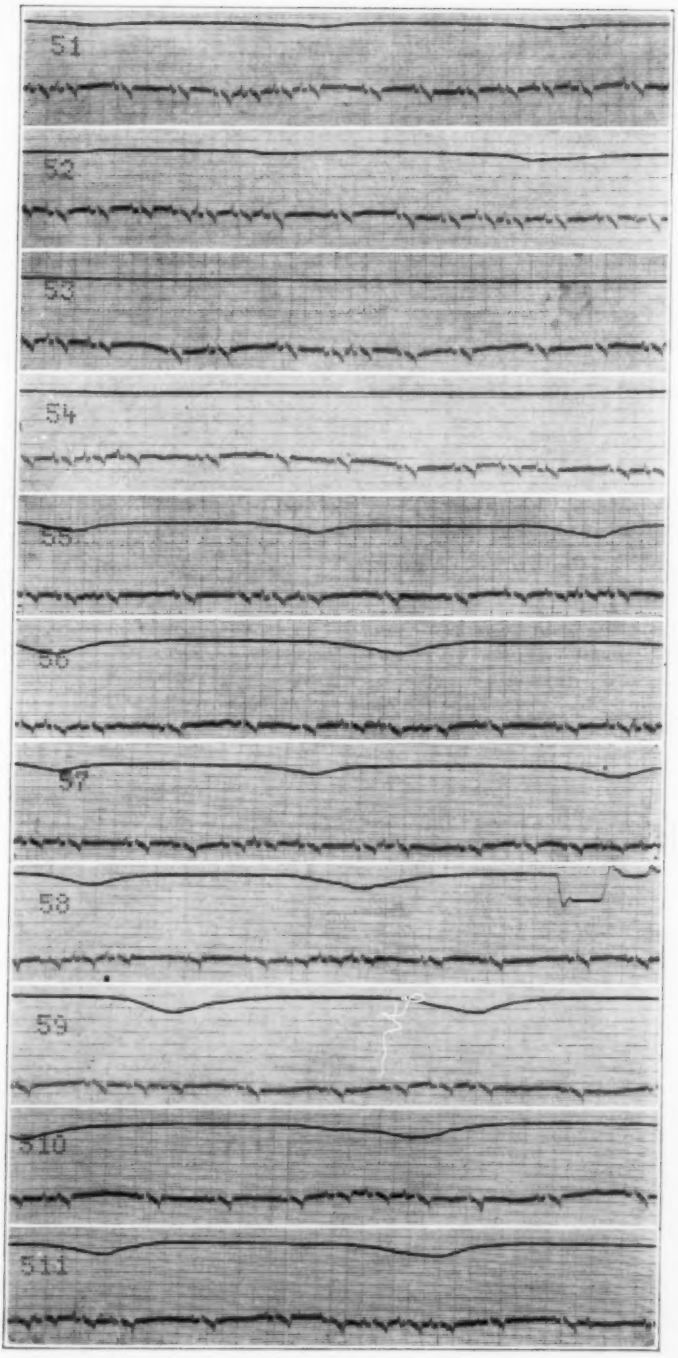

Fig. 7.—Sections of electrocardiograms (second lead), showing the effect of serum of morphinized dog in withdrawal, from which Table 6 was made.

ing to the methods of Folin and Wu [6] and of Van Slyke.[7] The blood used was obtained from the dogs and at the times described in Experiments, 2, 4, 5 and 6 of Table 7. Table 8 gives the results.

TABLE 8.—*Chemical Analysis of the Blood of Morphinized Dogs in Withdrawal*

	Dog 2, Mg.	Dog 4, Mg.	Dog 5, Mg.	Dog 6, Mg.
Nonprotein nitrogen	30.0	31.0	29.0	28.8
Urea	17.2	15.0	15.4	13.4
Creatinin	1.2	1.5	1.2	1.2
Uric Acid	1.0	1.0	2.3	2.0
Sugar	110.0	104.0	75.0	76.9
Whole blood chlorids	450.0	544.5	475.0	585.0
Carbon dioxid	52.2%	50.0%	52.0%	56.6%

The foregoing results are well within the range of normal dogs' blood.

COMMENT

Before comparing our results with those of Valenti, it may be desirable to make a few comments on his report. One of the features of his results to which he attaches great significance is the marked increase in range of variations in blood pressure and heart rate, after injection of the serum of a morphinized dog in withdrawal, as compared with the range in the normal period before injection. His method of obtaining this result from his records is to select the highest and lowest points, wherever they may occur in the normal period and in the period after starting the injection, respectively, and compare the differences. We find a few instances of errors made by him in the selection of these figures from his records (see Figures 1 and 2), but this does not affect the general nature of his results. In reporting that phase of our work, which was an attempt to duplicate his, we adopted the same method in order to permit of exact comparison, but we are unable to appreciate the significance of this particular feature of the results.

Examination of his tables shows that, in the majority of instances, the extreme high and low points of both the heart rate and blood pressure occur at various points in the progress of the experiment, and that both the heart rate and the blood pressure range up and down throughout the experiment, rather than following a definite and consistent course. It is hard to conceive of any substance which, when injected at a uniform rate into the veins of an animal, would be capable of producing such an irregular effect. Similar effects can be produced by substances which are rapidly absorbed and excreted, when not administered uniformly. It is well known that ether administration, when not under exact control, will produce these effects. It will be

6. Folin, O., and Wu, H.: J. Biol. Chem. **38**:81 (May) 1919.
7. Van Slyke, D. D.: J. Biol. Chem. **30**:347 (June) 1917.

noted that, as already stated, Valenti does not specify the form of anesthetic used in his experiments. It appears, however, that in his control experiments, using normal dog serum, he reports much smaller variations, and we are unable to offer any explanation of these observations. In our work, as will be seen from our tables, we obtained no results showing any substantial difference, as regards variability in heart rate or blood pressure, between the effects of the serum of a morphinized dog in withdrawal and those of normal dog serum. The slight differences occurring were more marked following the injection of normal serum.

Another feature of Valenti's reported results on which he lays much stress is the arrhythmia, which he states is produced by the injection of the serum of a morphinized dog in withdrawal. We have given sections of his tracing which he selected as showing three different types of arrhythmia. We have also given sections of our tracings for comparison. Our results do not correspond with his, as the tracing of our experiment with such serum shows no arrhythmia. The variations of rhythm shown in our tracing of the dog injected with normal dog serum are of the type obviously associated with respiratory changes.

The electrocardiographic method is, of course, much better adapted to show these features of the heart action than the mercury manometer, and it is naturally to be expected that if arrhythmia were produced it would be plainly apparent in the electrocardiograms. Our electrocardiographic studies show no abnormal arrhythmia. Such changes in rhythm as appear are, in the first place, uniform in all our electrocardiographic experiments, and, in the second place, clearly respiratory, as may be seen by comparison with the respiration curve. It is worthy of note that in the electrocardiographic experiments no anesthetic was used.

Valenti finds that the degree of circulatory disturbance produced by the injection of the serum of the morphinized dog in withdrawal is directly dependent on the total amount of morphin consumed during the addiction period. The largest total amount consumed by any of the dogs from which he obtained serum for injection was 69.95 gm. The serum in the experiments on the circulation presented by us was obtained from a dog that had received a total of 168.62 gm. If his conception is correct, our results should have been much more pronounced than his. The same reasoning applies in a measure to the question of the length of time of withdrawal of the morphin. While Valenti claims that the serum is equally effective when the blood is drawn at any time from thirty-six hours to twenty days after stoppage of morphin administration, we ascertained by electrocardiographic studies that there was a definite time at which the circulatory distur-

bances in the morphinized dog were at their maximum, and the serum used by us was obtained from blood drawn at that time.[8]

We feel that our work on cats and blood analysis is corroborative of our negative findings. We also feel that the conclusions reported in our first paper of this series have a definite bearing on the question now under discussion. We there reported that the serum of morphin addicted dogs and humans had no protective effect against a minimal fatal dose of morphin. If there was any toxic substance in the blood causing circulatory changes, which, as Valenti claims, could be neutralized in its physiologic effects by the administration of morphin, it is difficult to conceive the nature of such substance unless it is either chemically or physiologically an antidote to morphin. Our previous work shows conclusively that no such substance is present.

A notable point in Valenti's report is the statement that the circulatory disturbances in morphinized dogs can be suppressed, and the normal circulatory condition restored, at any time from thirty-six hours to twenty-one days after withdrawal, by administration of the previously accustomed daily dose of morphin. He emphasizes the fact that this effect cannot be produced by any amount less than the previous daily dose, and that it is only when this amount is exceeded that the typical "morphin pulse" becomes evident. Such persistence of tolerance as he reports is directly contrary not only to the generally known facts in the case of human beings, but also to the results of careful experiments on animals by competent investigators. Cloetta,[9] experimenting on rats and pigeons, found that these animals lost their tolerance as early as two days after the withdrawal and that the previous daily dose, if of a size fatal to a normal animal, proved fatal to these previously tolerant animals after this lapse of time. Van Egmond [10] showed that in dogs accustomed to tolerate 1 gm. of morphin daily the vagus center still responds to the injection of minute doses. He found it possible to change the heart rate from 120 to 80 per minute by a dose of 0.04 gm., while doses as small as 0.00008 gm. per kilogram in these same animals showed an appreciable effect. Van Dongen [11] and Tamura [12] also found that the vagus center does not become tolerant to morphin. In the course of our work, we found that profound general effects were pro-

8. We expect to discuss this question of changes in heart rate of the morphinized dog in withdrawal in a subsequent article. We are prepared to say at this time that we are satisfied that these changes are not due to any toxic substance in the blood.

9. Cloetta: Arch. f. exper. Path. u. Pharmakol. **50**:453, 1903.

10. Van Egmond: Arch. f. exper. Path. u. Pharmakol. **65**:197, 1911.

11. Van Dongen: Arch. f. d. ges. Physiol. **162**:54, 1915.

12. Tamura, O.: Physiol. Abstracts **6**:525, 1921.

duced by the injection, three days after the withdrawal, of a previous daily dose of 1 gm., and that these effects were noted very promptly, being quite pronounced within twenty minutes or less time.

We feel that Valenti's failure to give important details of his technic (e. g., the anesthetic used), the peculiar way in which he arrives at his conclusions by selection of figures from his records, and the impossibility of rationally reconciling his results with those of other workers who have investigated different aspects of the effects of morphin tolerance, and whose conclusions have met with general acceptance, lend weight to the conclusion to be drawn from the consistently negative results of our own work. We feel that our technic was such as to eliminate possible extraneous factors that may have influenced Valenti's results, and that the conditions under which our work was performed were even better calculated to obtain clear positive results from any toxic substance that might be present in the blood.

CONCLUSIONS

1. No toxic substance is formed in the blood of dogs habituated to morphin which is capable of producing circulatory disturbances in normal animals into which the serum is injected.

2. We find no evidence that any toxic substance is present in the blood as a result of morphin habituation.

CONGENITAL PERIPHERAL RESISTANCE; ITS CAUSATIVE RELATION TO THE PRECOCIOUS HYPERTENSIVE STATES*

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Until recently, hypertension was considered entirely the result of arterial and renal disease. Although the mechanism whereby such disease caused hypertension was unknown, the almost constant association of the symptom and such lesions seemed to justify such a conclusion. This was in accord with the still dominant tradition of the continental school; namely, that an abnormal function must necessarily be the result of a morphologic tissue change. It is becoming increasingly apparent, however, that an association of a lesion with a functional change does not always necessarily imply that this change is the result of the lesion. The lesion may represent an end-result of influences in which the functional change is the main or an important factor.

Correlation of pathologic evidence and clinical data furthermore revealed striking discrepancies: 1. Hypertension was present although at postmortem there was little evidence of arterial or vascular disease. Such cases are by no means rare. I reported five such, observed within a year.[1] 2. Renal and vascular disease, sometimes even marked, may be present, although the patient at no time had hypertension. Such cases may be said to be "normal" in patients past 55 years of age; these have been termed "decrescent arteriosclerosis and nephritis" by Clifford Allbutt. 3. There is no relation whatever between the grade of the hypertension and the extent and gravity of the arterial or renal lesion. These are serious obstacles to a rational explanation of hypertension on a renal or vascular basis and have in recent years again made the problem of the cause of hypertension an open issue.

What then is the relation of hypertension to disease of the renal and vascular systems? Evidence is accumulating that such lesions are the result of the hypertension itself, or better said, of the normal intravascular tension. Hypertension, which is merely an exaggeration of the normal tension, brings about such lesions earlier than they otherwise would occur. "Decrescent" lesions of kidneys and arteries are therefore the result of tension. The precocious and presenile lesions are the result of hypertension.

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1. Moschcowitz, Eli: Hypertension with Minimal Renal Lesions, J. A. M. A. **77**:1075 (Oct. 1) 1921.

This is not the place to discuss the arguments for this thesis. Those interested are referred to previous papers on this phase of the problem.[2]

In this conception, hypertension is not a "symptom" but the disease itself. In other words, function may not be interpreted in terms of anatomy, but reversely. As a matter of fact, our observations have shown that the clinical concept known as "essential hypertension" represents the earliest phase of cardiovascular renal disease. Conversely, most cases of arteriosclerosis and nephritis with hypertension at some time were cases of "essential hypertension."

Hypertension is a "disease" only on nosologic grounds. As far as our present methods of study permit us, a morphologic background is still lacking. Its genesis must be interpreted in terms of pathologic physiology rather than in those of anatomy.

In such an interpretation, an increase in peripheral resistance is the most important factor in the maintenance of an increased blood pressure in the general vascular system. Whether this resistance is in the peripheral portions of the arterial tree—the arterioles—as some aver, or in the capillaries; or whether the resistance is the result of functional or organic changes or both are problems that are as yet unanswerable.

The problem is clearer in regard to the cause of arteriosclerosis within the pulmonary circulation. Here, the peripheral resistance, in most instances, is a definite organic change, a stenosis of the mitral valve. Less often the increased intrapulmonary tension is the result of emphysema; chronic asthma and bronchitis, and narrowing of the main pulmonary trunks due to severe kyphoscoliosis. Arteriosclerosis of the pulmonary vessels and the associated lesion, which I have termed "arteriocapillary fibrosis" of the lung (Stauung's induration), a lesion analogous to arteriocapillary fibrosis of the kidney, practically never occurs unless such peripheral resistance is present.[2]

The direct cause, then, of the increase in peripheral resistance in the greater circulation is obscure. I have described[3] a "type" patient, a combination of psychic and physical characters, in whom hypertension is apt to occur. Such an individual may be best visualized as the antithesis of the child in psyche. The stresses and strains of our civilization and the consequent strivings for "success" do much to bring this about.

The physical characters of such individuals are partly hereditary and partly the result of the psychic makeup. The latter is probably responsible for the overweight. These people do not play or exercise. How psychic influences cause persistent increase in peripheral influences

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2. Moschcowitz, Eli: Pathology of Hypertension, J. A. M. A. **79**:1196 (Oct. 7) 1922.

3. Moschcowitz, Eli: Am. J. M. Sc. **158**:668 (Nov.) 1919.

is entirely speculative. We must know more of pathologic physiology of the blood vessels before this question can be answered.

In another group of cases, hypertension is the result of a persistent exophthalmic goiter. This is by no means an uncommon observation. It is well known that the tachycardia of exophthalmic goiter is associated with a normal or an elevated blood pressure. If the exophthalmic goiter persists over an extended period, the elevation of pressure may persist despite the eventual subsidence of other symptoms. In time, the classic evidences of clinical arteriosclerosis and nephritis develop. As the cause of exophthalmic goiter in most instances can be traced to emotional instability and psychic trauma, the relationship of psychic strain to hypertension cannot be lightly dismissed.

There, nevertheless, remains a large group of cases into which neither of these causes enter. We refer especially to cases of juvenile or presenile hypertension—cases in which hypertension occurs long before middle life, when hypertension is most commonly noted.

With the causes of pulmonary hyptertension still in mind, the problem presented itself as involving an investigation into the possibility of an organic increased peripheral resistance in these cases. A clue was given in the following case.

In 1920, Dr. B. S. Oppenheimer, at a clinical conference of Mount Sinai Hospital, presented a boy, aged 15, suffering from coarctation of the aorta. All the classic evidences of this lesion were manifest, subjective, physical and roentgenologic. The anastomotic internal mammary, scapular and vertebral arteries were enormous and tortuous. But there were other significant signs and symptoms. The blood pressure was 180 systolic; the urine contained albumin and casts; the radials and anastomatic arteries were hard and extremely tortuous.

This patient, therefore, suggested the following problem: Was the hypertension the result of the increased peripheral resistance existing, by an anomaly of nature, in the isthmus of the aorta, and was the manifest arteriosclerosis and chronic nephritis sequential to the hypertension? Or was the association of the hypertension and the attendant lesions merely casual and without bearing on the coarctation?

As the rarity of coarctation of the aorta did not offer much prospect of immediate observation with these issues in view, a recourse to the literature on coarctation of the aorta was necessary. It soon became apparent that there were certain deficiencies in observation. 1. The vast majority of the observations antedate the discovery of the sphygmomanometer. 2. Either clinical data are insufficient or a precise morbid anatomy is wanting. Nevertheless, the mass of available data furnishes sufficient evidence to show that hypertension and the associated arteriosclerosis and nephritis are common sequelae to congenital narrowing of the aortic isthmus.

In 1872, Eppinger[4] reported two cases: In the first, in a woman of 61, contracted kidneys were revealed at necropsy. In the second, in a youth, aged 17, who died of cerebral hemorrhages, the kidneys were "small, firm and tough."

In 1897, Schichold[5] reported the case of a woman, aged 32, who since childhood suffered from dyspnea, palpitation, and edema of the legs. The temporal arteries were tortuous; the left ventricle was enlarged, and there was present an aortic insufficiency. At necropsy, the aortic valves were greatly thickened and covered with warty vegetations; the root of the aorta was much thickened. It revealed profound arteriosclerosis and was elongated. The findings in other organs are not mentioned.

In 1900, Schlesinger[6] reported the case of a man, aged 50, with cardiac symptoms and the typical collateral circulation of the internal mammary arteries. The vertebra and the subscapular arteries were much "thickened and elongated."

In 1901, Minkowski[7] reported a patient, aged 23, whose blood pressure was 300 (Riva-Rocci) and whose kidney function was normal.

In 1901, Bandel[8] reported the case of a man, aged 19, whose blood pressure was normal. The aorta was profoundly sclerotic. The kidneys, grossly, showed only congestion.

In 1902, Reinitz[9] reported two cases: 1. A man aged 34, suffered sudden death from apoplexy. The aorta was sclerotic; the right kidney was large and smooth, and revealed good markings (no microscopic examination). The left kidney was absent. 2. A man, aged 37, committed suicide. The aorta was sclerosed, more markedly below than above the isthmus. The condition of kidneys is not mentioned.

In 1903, Haberer[10] reported the case of a woman, aged 47, in whom there was complete obliteration of the aorta. "The blood pressure was enormously increased." There was marked general arteriosclerosis, especially of the collateral vessels. The aortic valves were adherent. The kidneys showed parenchymatous degeneration.

In 1905, Fawcett[11] reported eighteen cases. Two were diagnosed as chronic nephritis, but a reading of the histories would justify the inclusion of a number of others; most of the cases were in young or middle aged persons. Arteriosclerosis, especially of the collaterals, was present in practically every case. The necropsy protocols on the kidney lesions are poorly presented and microscopic reports are lacking.

In 1907, Mönckberg[12] reported a marked sclerosis of the aortic valves in a patient, aged 50, which he believed was the result of hypertension.

In 1918, Paillard[13] reported the case of a youth, aged 17, with marked hypertension in upper extremities. There was no necropsy.

In 1919, Lommel[14] reported the case of a woman, aged 38, in whom the collateral vessels were thickened and tortuous. The blood pressure was 190. There was no necropsy.

In 1920, Hart[15] reported the case of a man, aged 42. There was no blood pressure determinations. The collaterals showed profound arteriosclerosis.

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4. Eppinger: Prag. Vierteljahrschr. **112**:31, 1872.
5. Schichold: München. med. Wchnschr. **44**:1279, 1917.
6. Schlesinger: Internat Clinics **55**:140, 1900.
7. Minkowski: München. med. Wchnschr. **48**:1335, 1901.
8. Bandel: Deutsch. Arch. f. klin. Med. **72**:381, 1901.
9. Reinitz: Inaug. Dissert., Kiel, 1902.
10. Haberer: Ztschr. f. Heilk. **4**:26, 1903.
11. Fawcett: Guy's Hosp. Rep. **59**:1, 1905.
12. Mönckberg: Verhandl. d. Deutsch. path. Gesellschr. **11**:224, 1907.
13. Paillard: Thése, Paris, 1918-1919.
14. Lommel: Med. Klin. **15**:892, 1919.
15. Hart, C.: Med. Klin. **16**:1337 (Dec. 26) 1920.

In the same year, Moon [16] reported the case of a boy, aged 11, with marked thickening and rigidity of the edges of the aortic valves, giving rise to regurgitation.

In 1921, Follet and Caillé [17] reported the case of a youth, aged 17, with hypertension in the arms and very low pressure in the legs.

In 1922, Edelmann [18] reported the case of a man, aged 25, whose blood pressure was 195 systolic; 45 diastolic. The collateral vessels were thickened and tortuous. No necropsy was performed.

Lanbry and Morre,[19] in 1916, reported the case of a man, aged 29, in whom "the blood pressure was high."

These citations, which include the majority of case reports furnishing the necessary data on this problem, indicate that hypertension, arteriosclerosis and nephritis are very frequent sequelae of congenital stenosis of the aorta. This is especially noteworthy, since the majority of these patients had not reached the period of middle age. All observers are agreed that sclerosis of the valves and of the aorta below the point of stenosis are constant findings and that the aortic ring is consequently often insufficient. Indeed, rupture of the aorta due to the increased tension is not an uncommon end (Huchard).[20] As further circumstantial evidence that hypertension must be commonly present is the fact that apoplexy is a common mode of death in this condition (Minowski,[7] Brunner [21]).

One must not carry away the impression that every case of congenital stenosis of the aorta is followed by hypertension and its attendant pathologic phenomena. Cases have been reported in which hypertension was not present (Strassner [22]). Patients with this anomaly have been known to live to an advanced age, in one case to the age of 92. A normal or low tension may be explainable in one or two ways: 1. A previously existent high blood pressure became low as the result of cardiac decompensation. 2. The peripheral resistance was equalized by an unusually rich anastomosis (internal mammary, intercostal, vertebral and subscapular arteries).

CONGENITAL NARROWING OF THE AORTA (AORTA ANGUSTA)

A disproportion between the quantity of blood and hypoplasia of the vascular system will give rise to an increased peripheral resistance.

The concept of congenital hypoplasia of the aorta was introduced by Virchow,[23] who associated this lesion with chlorosis. Since then, the

16. Moon, R. O.: Lancet **1**:1314 (June 19) 1920.
17. Follet and Caillé: Arch. d. mal. du cœur. **14**:207 (May) 1921.
18. Edelmann, A., and Moron, R.: Wien. Arch. f. inn. Med. **4**:1 (April) 1922.
19. Lanbry and Morre: Bull. et mém. Soc. méd. d. hôp. de Paris **40**:2237, 1916.
20. Huchard: Traites des maladies du cœur et l'aorte, Paris, 1908.
21. Brunner: Deutsch. med. Wchnschr. **24**:794, 1898.
22. Strassner: Deutsch. Arch. f. klin. Med. **95**:344, 1909.
23. Virchow: Ueber die Chlorose, Berlin, 1872.

study of the narrow aorta has been rather extensive, and it has been noted with a variety of conditions; e. g., phthisis, status thymicolymphaticus, chlorosis, acromegaly, hypoplasia and hypertrophy of the heart, pernicious anemia and purpura hemorrhagica. A study of the literature on narrow aorta leaves one rather confused. In the first place, there is no absolute criterion as to what constitutes a narrow aorta. Beneke,[24] for instance, in a series of 100 necropsies, found a wide range. At a distance of 1 cm. above the valve, the circumference varied between 58.8 and 31.0 mm.; in the middle of the thoracic aorta, between 40.7 and 13.2 mm., and at a point 3 cm. above the bifurcation, between 33.3 and 13.2 mm. He found the diameter larger in males than in females, and there was an approximate relationship to the height and age of the individual. Scheel's[25] figures are somewhat higher. For instance, between the ages of 20 and 30, the circumference of the ascending aorta averages between 62 and 57 mm. On the other hand, Strassburger[26] and Suter[27] claim that the width of the aorta as measured postmortem is no criterion as to its carrying capacity during life. They hold that elasticity and distensibility of the coats vary widely and that a presumably narrow aorta may become sufficiently wide under the normal intravascular tension.

Furthermore, the association of narrow aorta with some of the conditions above described has been questioned. Thus, in a recent critique, Louise Kaufmann[28] doubts whether a narrow aorta has any pathologic significance whatever. Her material is rather limited, being confined to young and middle aged soldiers. She studied the association of narrow aorta with phthisis and status thymicolymphaticus, and found that such individuals possess aortas with diameters within the normal range. Her findings in status thymicolymphaticus are in conflict with most of the testimony of other able observers, notably Stoerk[29] and Kolisko.[30]

Whatever the significance of narrow aorta may be, the fact remains that (1) there exists a uniform relative diminution in size of the aorta from the root to the iliac bifurcation; (2) the size of the aorta is fairly uniform for the age and height of the individual; (3) an aorta may be regarded as definitely narrow when it is at least from 5 to 10 mm. smaller at a point 1 cm. above the root than the mean averages compiled from the Beneke, Scheel and Kaufmann tables.

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24. Beneke: J. f. Kinderkr. **4**:380, 1871.
25. Scheel: Virchows Arch. f. path. Anat. **191**:135, 1908.
26. Strassburger: Frankfurt. Ztschr. f. Path. **3**:283, 1909.
27. Suter: Arch. f. exper. Path. u. Pharmacol. **39**:289, 1897.
28. Kaufmann: Zur Frage der Aorta angusta, Jena, 1919.
29. Stoerk: Zur Klinik der Lymphatismus, Berlin, 1913.
30. Kolisko: Quoted by Stoerk (Footnote 29).

It is conceivable that a narrow aorta may furnish sufficient peripheral resistance to cause hypertension and its consequences, arteriosclerosis and nephritis, and thus explain the genesis of hypertension in cases otherwise obscure; for instance, juvenile and precocious hypertension. The first young nephritic on whom we had occasion to perform a postmortem examination gave, in a striking fashion, expected findings.

REPORT OF CASE

History.—M. K., aged 42, a driver, whose family and past history was irrelevant, for two and a half weeks had felt weak. There were general malaise, dyspnea and a dry cough. Five days before, there was epistaxis which lasted four days. Nocturia was present.

Examination.—The patient had sonorous and moist râles at both bases. The apex of the heart was not visible. Maximum intensity of the sounds was in the fifth space, 1½ inches (3.7 cm.) within the mammary line. The second aortic sound was accentuated. The sounds were regular, and there were no murmurs. The radial arteries were thickened. The urine contained a heavy trace of albumin and the specific gravity varied between 1.017 and 1.023. Hyaline and granular casts were present. The phenolsulphonephthalein output in two hours was 12 per cent. The quantity averaged around 25 ounces (750 c.c.). The blood pressure during his stay varied between 190 and 248 systolic and 130 and 160 diastolic. The blood chemistry tests on admission showed urea, 23.0; nonprotein nitrogen, 48.7; creatinin, 1.5; glucose, 0.105. These figures rose steadily until twelve days later, when the urea was 60.6; nonprotein nitrogen, 79.3; creatinin, 2.0; glucose, 0.15. The retina and optic disk were edematous; the margins were indistinct. The veins were dilated, the arteries thin and in places invisible. There were hemorrhages along the vessel and the disk.

Necropsy.—The lungs showed an old healed pleural tuberculosis of the right apex. Both bases were intensely congested and slightly edematous; the remainder of the lungs otherwise showed passive congestion. The heart was very large. The left ventricle was enormously dilated. There was marked hypertrophy, and the aortic valve was slightly rigid. The mitral valve was normal. There were some atherosclerotic patches on the upper inner wall of the left ventricle. The muscle was firm and brownish red. The aorta was markedly sclerosed and inelastic. The right ventricle was dilated. The pulmonary artery was smooth. The liver which showed advanced change of the nutmeg type weighed 1,360 gm. The spleen weighed 68 gm. and was slightly enlarged, firm and a deep purple. The pancreas was enlarged and firm. The left kidney weighed 89 gm.; the right, 140 gm. The capsule stripped easily. The surface was markedly granular. On section, the appearance was mottled; the cortex was thin, and the markings were very poor. The blood vessels were prominent.

Diameters, of the vascular system: The ascending aorta, 1 cm. above the ring, measured 42.7 mm.; the thoracic aorta, 34.5 mm.; the common iliac artery, 15.7 mm.; celiac axis, 12.6 mm.; splenic artery, 6.3 mm.; renal artery, 12.6 mm.; innominate artery, 22.0 mm.; common carotid artery, 12.6 mm.; pulmonary artery, 57.5 mm.

Anatomical diagnosis: Hypoplasia of the vascular system; chronic diffuse nephritis (arteriocapillary fibrosis); chronic congestion of the lungs with hypostasis; hypertrophy and dilatation of both ventricles, and chronic congestion of the spleen were diagnosed.

Microscopic Examination.—The heart showed hypertrophy of the muscle fibers. There was brown pigmentation of the heart muscle and slight interstitial myocarditis. The lungs showed chronic passive congestion, and the spleen showed chronic congestion. The kidneys presented a diffuse growth of connective tissue, especially in the cortex. The glomeruli were shrunken, many showing connective tissue transformation with hyalinization and occasional calcification. The Bowman capsules were slightly thickened. The tubules were deformed and in connective tissue areas were either absent or few and small. In other areas, they were numerous and enlarged (compensatory hyperplasia). The blood vessels were thickened and showed intimal hyperplasia and connective tissue thickening.

In the meantime, investigation revealed a surprisingly comprehensive literature dealing with this topic.

Virchow,[30] in 1872, was apparently the first to note the association of early arteriosclerosis and nephritis with narrow aorta, but credit is due to Lancereau [31] and his pupils, Besancon [32] and Mosgofian [33] for the introduction and systemic study of this conception.

Lancereaux believes that the majority of nephritides in the young and the so-called hereditary nephritides are the result of congenital aplasia of the vascular system. His description of the clinical picture corresponds precisely to that associated in our minds with nephritis with hypertension; and the necropsy findings likewise reveal contracted kidney. The kidneys are small (from 45 to 80 gm.) and granular; the capsule is adherent, and the cortex is thin and contains cysts. Microscopically, there is enormous connective tissue increase with sclerosis of the vessels and glomeruli. Many patients give a history of chlorosis, and present evidences of infantilism. It is interesting to note that, from the point of view of pathogenesis, Lancereaux, even in the eighties, believed that increased intravascular tension was the cause of the condition.

Bensancon's discussion is in a similar vein. He reports nine cases, varying between the ages of 18 and 35; in the four cases in which measurements were made, the diameter of the aorta at the root was 44, 42, 52 and 42 mm. Mosgofian, again, covers practically similar ground and reports eight cases, the patients varying in ages between 17 and 37. Indeed, he asserts that these cases are by no means uncommon. Subsequent writers (Fräntzel,[34] Luzet [35] Spitzer,[36] Chiaruttini [37] Moutard,

31. Lancereaux: Gaz. Med. de Paris **7**:172, 1891; Lecons de Clinique Medicales Paris, 1894; Diction. Encyclopedique des Sci. Med. Paris, 1875, p. 196.
32. Besancon: D'une nephrite liée a l'aplasie arterielle, Paris, 1889.
33. Mosgofian: Thése, Paris, 1893.
34. Fräntzel: Berl. klin. Wchnschr. **25**:575, 1888.
35. Luzet: Arch. gen. de méd., 1890, p. 725.
36. Spitzer: Wien. med. Wchnschr. **47**:1602, 1897.
37. Chiaruttini: Clin. med. ital. **38**:481, 1899.

Martin and Bacalogene,[38] Burke,[39] Romberg[40] and Apelt[41]) report a considerable number of cases, but add practically nothing new to Lancereaux's observations. Approaching the era when blood pressure determinations become routine, Wolkow[42] describes rigidity of the radial arteries in young individuals of the gracile chlorotic type, associated with hypertension and signs of cardiovascular-renal disease, who at necropsy presented a narrow aorta. Müller[43] describes war recruits with rigid arteries and a drop heart associated with a narrow aorta. The most recent paper is by Strauss,[44] who also found recruits in the second and third decades with high blood pressure, hypertrophy of the left ventricle, rigid arteries and a narrow aorta. He attempts a clinical explanation of the condition and believes that an otherwise unexplainable hypertrophy of the left ventricle with arteriosclerosis in a young individual is suggestive of the presence of a narrow aorta.

These citations certainly show that cardiorenal disease especially in the young is frequently associated with narrow aorta. It does not follow that every young patient with an unexplainable nephritis possesses a narrow aorta. A recent necropsy, in the case of a man, aged 20, with cardiovascular disease, showed, for instance, an aorta of normal dimensions. It was thought that a perusal of the literature on hypertensive nephritis in childhood would afford corroboration of our thesis, but aside from some suggestive data, this proved unsatisfactory for the reason that the size of the aorta is ignored. Barlow[45] and Brault[46] mention the small size of the vessels in their cases of juvenile arteriosclerosis.

In this connection, certain observations in juvenile nephritis are significant as an indication that a maldevelopment of a hypoplastic nature is a factor in the condition. This may also explain cases of familial nephritis. Brill and Libman[47] report the case of a child of 14 with interstitial nephritis and arteriosclerosis, who was weak and undersized. The other children in the family had nephritis. Miller and Parsons[48] report cases of interstitial nephritis in children who presented a general aplasia. One child, aged 9, was the same size as his brother, aged 3.

38. Moutard, Martin and Bacalogene: Bull. et. mém. Soc. méd. d. hôp. de Paris **15**:110, 1898.
39. Burke: Deutsch. Arch. f. klin. Med. **71**:189, 1901.
40. Romberg: Lehrb. des Krankheiten des Herzens u. Blutgefasse, Berlin, 1906.
41. Apelt: Deutsch. med. Wchnschr. **31**:1186, 1905.
42. Wolkow: Verhandl. Kong. f. inn. Med. **27**:611, 1910.
43. Müller: Med. Klin. **11**:1365, 1915.
44. Strauss: Med. Klin. **12**:416.
45. Barlow: Lancet **2**:151, 1874.
46. Brault: Arterites et Scleroses, Paris, 1897.
47. Brill and Libman: J. Exper. Med. **4**:541, 1899.
48. Miller and Parsons: Brit. J. Dis. Child. **9**:289, 1912.

He calls the condition "renal infantilism." Barker [49] reports two cases in the same family, both in children much undersized. He subscribes to the previously mentioned conception of "renal infantilism." Hill [50] reports a case of chronic interstitial nephritis with hypertension in a child with infantilism.

In a recent paper, Evans [51] reports four cases of arteriosclerosis in children, all suffering from hypoplasia. The familial tendency of juvenile arteriosclerosis and nephritis is commented on by most observers. These evidences, while few, are suggestive, and the deficiencies in our observations are only too evident.

Much work is necessary on the problem of juvenile or presenile arteriosclerosis and nephritis along the lines suggested in this paper before we can attain a correct knowledge of the statistical relationship of congenital peripheral resistances to hypertension and its sequences, arteriosclerosis and nephritis.

CONCLUSIONS

1. The immediate cause of hypertension is unknown.

2. Among the remote causes, psychic factors play an important rôle. Evidence of this is presented in two varieties of individuals in whom hypertension is a common occurrence: (*a*) the "type" individual described in a previous paper, who may be summarized as the antithesis of the "child" in makeup and temperament; (*b*) patients with the incomplete or complete forms of exophthalmic goiter or "autonomic imbalance" in whom accumulating evidence shows that psychic and emotional factors are of importance in their causation.

3. Peripheral resistance is of importance in the causation of hypertension and its consequences, arteriosclerosis and nephritis. In the lesser circulation, this is proved by the fact that, in cases of mitral stenosis, even in young individuals, marked arteriosclerosis of the pulmonary vessels and "arterio-capillary fibrosis" (Stauungs' induration) of the lung are present; while the systemic arteries in cases of general vascular hypertension show arteriosclerosis, the pulmonary vessels are free.

4. There is evidence that a congenital peripheral resistance, either in the form of congenital stenosis of the isthmus of the aorta or a congenital narrow aorta (aorta angusta), may be the cause of hypertension, arteriosclerosis and nephritis. This may account for the etiology of some cases of juvenile or presenile arteriosclerosis and nephritis and some cases of familial nephritis.

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49. Barker: Brit. M. J. **2**:1204, 1913.

50. Hill, L. W.: Nephritis of Children, Am. J. Dis. Child. **17**:270 (April) 1919.

51. Evans, G.: Quart. J. Med. **16**:33 (Oct.) 1922.

THE METABOLISM-PULSE RATIO IN EXOPHTHALMIC GOITER AND IN LEUKEMIA

WITH REMARKS ON CERTAIN SIMILARITIES IN THE SYMPTOMATOLOGY OF THESE DISEASES *

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AND

JAMES HOWARD MEANS, M.D.

WITH THE ASSISTANCE OF CONSTANCE HOPKINS

BOSTON

Experiment, as shown by Galen, consists of "putting questions to Nature and arranging matters so that Nature may answer them." The question we have asked is: What causes the rapid pulse in hyperthyroidism? Is it dependent solely on the increased metabolic rate or is there invariably some other factor that produces tachycardia?

This question cannot be answered directly. However, it occurred to us that light might be thrown on the subject by a comparison of the relation between basal metabolism and basal pulse rate in hyperthyroidism with that in leukemia. These are the two afebrile [1] morbid states that are conspicuously characterized by an increased rate of heat production.

For the purpose of comparison, a plot has been made of the basal metabolism rate (ordinates) against basal pulse rate (abscissae) for 180 observations in 126 cases of exophthalmic goiter (Chart 1) and for 110 observations [2] in seventy-one cases of chronic leukemia (Chart 2). Of the latter patients, forty-five had myelogenous and twenty-six lymphatic leukemia.[3] A similar comparison has been made by Sturgis [4] in exophthalmic goiter, with results similar to those

* From the Medical Services of the Massachusetts General Hospital and the Collis P. Huntington Hospital of Harvard University. This paper is No. 8 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

1. Fever of course occasionally occurs in leukemia, especially when the disease is very active. Under such circumstances, a metabolic rate increment due to fever is probably superimposed upon that due to the disease per se.

2. We are indebted to Dr. James Hitchcock for making some of the determinations.

3. No difference in ratio was found in the two forms of chronic leukemia.

4. Sturgis, C. C., and Tompkins, E. H.: A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, Arch. Int. Med. **26**:467 (Oct.) 1920.

recorded below. Our observations were all taken when the patients had no fever. The basal pulse and basal metabolism observations represented by each point were simultaneous, when more than one observation was used in a given case, they were obtained on different days, usually some weeks apart. The results are shown in Charts 1 and 2. The general distribution of the dots is similar in the two. The distribution, however, at first appeared to be so wide that some doubt was had as to the propriety of drawing any conclusion from the data. They were therefore submitted for statistical study to Dr. W. T.

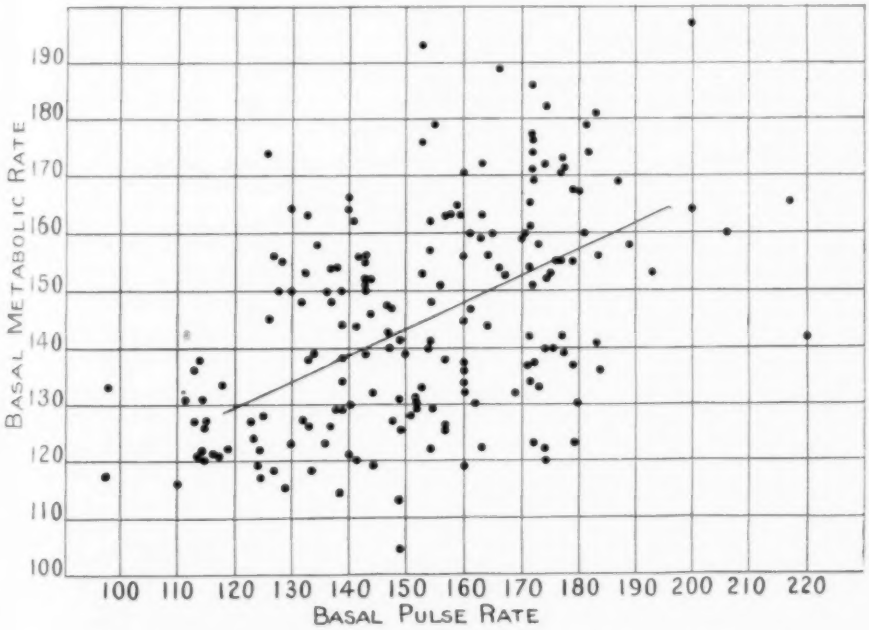

Chart 1.—Exophthalmic goiter: In this and in Chart 2, the basal metabolic rate is plotted against the basal pulse rate. For convenience in the two charts, the basal pulse rate is expressed in percentage of normal as is the metabolism, instead of as beats per minute. The rate of 60 per minute was taken as normal for men, 70 for women, and each expressed as 100 per cent. The normal basal metabolic rate is also expressed as 100 per cent. The diagonal line is a smoothed curve representing the average distance of the dots above the base line.

Bovie, who found that there was a high degree of correlation between the data for basal pulse and basal metabolism in both diseases; the correlation coefficient in exophthalmic goiter being 0.525 ± 0.036 and in leukemia 0.544 ± 0.044. Furthermore, the ratios in the two diseases were essentially the same. A smoothed curve representing the average

height above the base line is shown in each chart. This is of necessity at best only an approximation, but the similarity in the slopes of the two is striking.

These observations indicate that, for a given basal metabolic rate increase, there is about the same degree of pulse elevation in chronic leukemia as there is in exophthalmic goiter. In hyperthyroidism, certain circulatory abnormalities are regarded as cardinal symptoms of the disease; in leukemia, they are not generally so regarded. If the tachycardia of leukemia is purely a resultant of increased metabolic

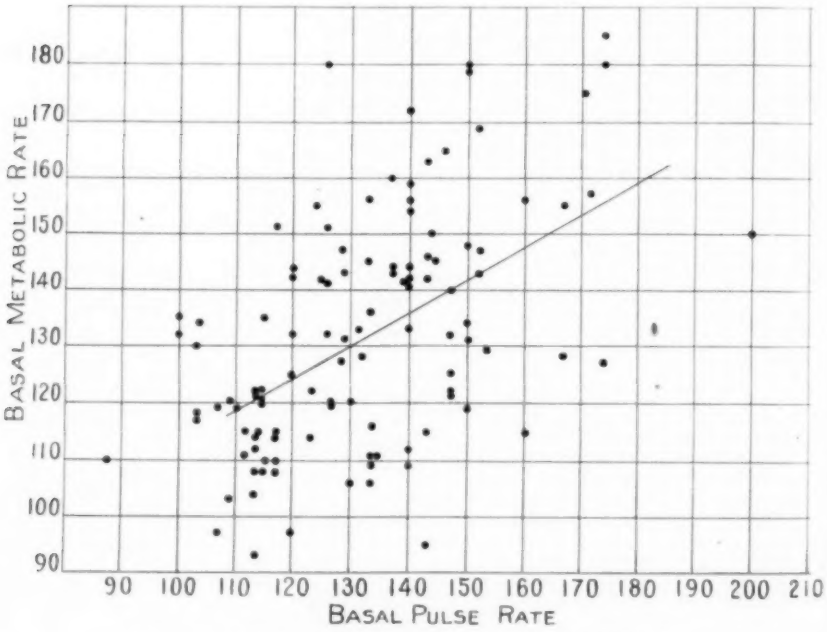

Chart 2.—Chronic Myelogenous and Lymphatic Leukemia.

rate, that of exophthalmic goiter may well be considered as due to the same cause. We do not wish to imply that there never is any extrametabolic factor in the production of the increased pulse rate of hyperthyroidism or leukemia. It is well recognized that there often is cardiac damage in hyperthyroidism of sufficient degree to be undoubtedly capable of increasing the tachycardia; while in leukemia, anemia may do the same. Anemia may also give rise to some degree of cardiac insufficiency. Even so, we believe it is a reasonable conclusion from the data given that, in the majority of uncomplicated cases of exoph-

thalmic goiter, the increased metabolism is at least sufficient to account for the tachycardia observed. This conclusion is permissible provided the assumption is sound that there is no frequent important cardiac factor in leukemia. The rareness of cardiac insufficiency in the latter disease, except as a late manifestation associated with profound anemia, suggests that this is so. Some cardiac enlargement in exophthalmic goiter is not infrequent,[5] and from our observations of fifteen cases, it appears that the hearts of persons dying from leukemia are on the average 75 gm. overweight. A similar condition is found in persons who have suffered from anemia for years.[6] Such cardiac hypertrophy presumably results from the long continued overwork by the heart and is not to be regarded as the primary cause of the tachycardia.

The symptomatology of the hyperthyroidism is peculiarly interesting, in that, as pointed out by Du Bois,[7] it can largely be explained on the basis of the known functional pathology. The increased rate of heat production, together with an essentially normal body temperature, directly explains the sensation of warmth, the increased sweating and the flushed, moist skin, these being due to increased heat elimination. The loss of weight is a direct expression of increased heat production, and the excessive appetite an attempt on the part of the organism to compensate for this. The tachycardia, as stated above, may result from increased metabolism alone. The dyspnea in hyperthyroidism can also probably be explained without assumption of a primary cardiac factor. Certain of the nervous system symptoms, such as irritability, tremor and asthenia, and such symptoms as the eye signs, diarrhea and menstrual disturbances, cannot be directly explained on the basis of increased metabolism. They may occur as noted by Kessel and Hyman [8] in persons with normal metabolic rates, as may neurogenic tachycardia also.

If the first category of symptoms given is, in hyperthyroidism, a direct expression of increased heat production, then in leukemia, even when afebrile, one would expect to find these same symptoms. Statistical data concerning these symptoms in leukemia are at present not available but are in the process of compilation. However, it is evident

5. Willius, F. A., and Boothby, W. M., with a note on the pathology by Wilson, L. B.: The Heart in Exophthalmic Goiter and Adenoma with Hyperthyroidism, Med. Clinics N. America **7**:189 (July) 1923.

6. Cabot, R. C., and Richardson, O.: Cardiac Hypertrophy in Pernicious Anemia, J. A. M. A. **72**:991 (April 5) 1919.

7. Du Bois, E. F.: Metabolism in Exophthalmic Goiter, Arch. Int. Med. **17**:915 (June) 1916.

8. Kessel, Leo, and Hyman, H. T.: Studies of Graves Syndrome and Involuntary Nervous System; Clinical Manifestations of Disturbances of Involuntary Nervous System (Autonomic Imbalance), Am. J. M. Sc. **165**:513 (April) 1923.

from the literature,[9] as well as from our study of leukemia, that many of these symptoms are commonly observed in this disease. Leukemic patients quite constantly experience a sensation of warmth and show a distinct tolerance for cold in spite of anemia and emaciation. Increased sweating is not uncommon; a warm moist skin is often observed, and hot moist hands characteristic of exophthalmic goiter are not infrequent in leukemia. Flushing seems much less usual than in hyperthyroidism. Loss of weight, which often is marked and rapid, is a feature of leukemia, and many of these patients without gastro-intestinal complications have an increased desire for food. Dyspnea is common in both diseases, and while in leukemia, anemia plays a part, the increased metabolic rate in the two would seem to be an important factor in its production.

Nervousness, irritability, insomnia and tremor, symptoms of hyperthyroidism that are probably not directly due to increased metabolic rate, are not common in leukemia. The three former symptoms may occur in leukemia as in other chronic diseases; while we have observed occasionally a slight fine tremor when the disease is advanced and the hemoglobin considerably reduced. The eye signs observed in exophthalmic goiter are lacking in leukemia, though, as a great rarity, unilateral exophthalmos has been observed presumably due to leukemic infiltration or hemorrhage into the orbit. Persistent diarrhea does occur in leukemia, and not infrequently when many immature cells appear in the circulation. Menstrual irregularities may occur but are not prominent. Lack of strength or a sense of undue fatigue is one of the commonest symptoms to indicate to the patient with leukemia his ill health. However, it is more a lack of strength than a true myasthenia as seen in hyperthyroidism.

CONCLUSIONS

1. The amount of pulse elevation for a given metabolic rate elevation is essentially the same in hyperthyroidism and in chronic leukemia. From this, it is inferred that in both diseases the tachycardia is chiefly the result of an increased metabolic rate.

2. Certain symptoms of hyperthyroidism which are believed to be the direct expression of an increased metabolic rate also occur in leukemia, a disease likewise invariably characterized by increased heat production.

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9. Ordway, T., and Gorham, L. W.: Leukemia, The Oxford Medicine **2**:681, New York, Oxford University Press, 1920. Vogel, K. M.: The Leukemias, Nelson Loose-Leaf Medicine **4**:66, New York, T. Nelson and Sons, 1920. Cabot, R. C.: Leukemia, Osler and McCrae's Modern Medicine **4**:659, Philadelphia, Lea and Febiger, 1915. Naegeli, O.: Leukämien Blutkrankheiten und Blutdiagnostik, Lepsic, Veit and Company, 1912.

AN ANATOMIC AND CHEMICAL REPORT ON A UNIQUE CASE OF MYELOMA *

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A careful scrutiny of the literature shows that only about seventy-seven cases of multiple myeloma have been reported to date (January, 1922). Eight of these were reported from Maryland alone. The two reported from California were observed in this laboratory. I may add that I know of a third case which occurred in one of the hospitals for the insane in this state. That the total number of cases observed is still small is shown also by the fact that Kahn [1] estimated that only sixty-one cases had been reported in 1914. The rareness of this condition would seem to be further emphasized by the fact that Symmers and Vance [2] (1918) found only three cases among 2,000 necropsies at Bellevue Hospital. It should be mentioned that Vance [3] (1916) verified ninety-eight references on myeloma, but that does not imply that the articles concerned the same number of cases. It is true that a single article sometimes covers several cases, but the reverse also happens. Hence, it would seem that even the anatomist should not consign an incidental discovery of a case to oblivion; especially not when, as in the case reported here, the anatomic findings are unique in at least two respects. Furthermore, if attention is called to every additional case, a smaller number will be overlooked or go unrecorded in the future. Had attention been directed to the possibility of the existence of this condition, the cases reported from this laboratory would have been detected by clinicians. Either case could easily have been recognized positively by a roentgen-ray examination months before death. Perhaps it should be said that, according to Beck and McCleary [4] (1919), "roentgenologically no definite bone changes were demonstrable" when their patient was first seen. Since swellings in both clavicles and one in the first rib, said to have measured 5 cm. in diameter, were present, this statement is very perplexing. Pepper and Pearce [5] (1917) also stated

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* Anatomic report by Dr. Meyer, Chemical by Dr. Cajori.

1. Kahn, H. M.: Four Cases of Multiple Myeloma, Med. Rec. **85,** 1914.

2. Symmers, Douglas, and Vance, M.: Multiple Intravascular Hemangioendotheliomata of Osseous System with Systems of Multiple Myeloma, Am. J. M. Sc. **152:** 28 (July) 1916.

3. Vance, B. M.: Multiple Myeloma, Nature and Origin, Am. J. M. Sc. **152:**693 (Nov.) 1916.

4. Beck, H. G., and McCleary, S.: Multiple Myelomas with Bone Marrow Plasma Cells in the Blood; Report of Case, J. A. M. A. **72:**480 (Feb. 15) 1919.

5. Pepper, O. H. P., and Pearce, R. M.: Myeloma with Metastasis to Liver and Spleen, J. M. Research, Bost. **37:**171-182 (Sept.) 1917; Proc. Path. Soc. Phila. **38:**11, 1918.

that the roentgen ray did not reveal the presence of osseous lesions in their case, although the compacta was only 0.5 mm. thick and the pelvis, vertebrae and ribs were all involved by the disease. Failure of the roentgen ray to reveal the disease was attributed to its very diffuse form by these investigators. While this no doubt is an important factor, it would seem that, even when present in very diffuse form, the great thinning of the compacta which the disease sometimes effects should become evident in the roentgenograms as in the present cases and in Turner's [6] (1921) cases.

A perusal of the later literature seems to indicate that there is an increase in the number of cases showing the presence of extraskeletal lesions. It must be clear, however, that if we are to regard the myelomatous condition as myeloblastic in origin, tumors in the kidneys, muscles, liver, fat, ovaries, lymph nodes, tonsils, etc., must be regarded as true metastases. Symmers and Vance regarded their Case 2 and that of Christian [7] (1907) as the only cases with true metastases. Since then, other cases have been reported, and Pepper and Pearce [5] discussed fifteen cases of probable metastases, only eight of which they regarded as doubtful. Morse [8] (1920) also reported a case with metastases.

The probable duration of the disease was lengthened by reports on later cases, and pain seems to be given more prominence as an early symptom. Dyspnea or a hacking cough are more commonly mentioned. Arteriosclerosis seems to have been present in pronounced form in a number of cases, some of which, as those of Meyer and Swain [9] (1918) and Beck and McCleary, also showed dilatation of the aortic arch. Since calcium phosphate is not infrequently deposited even in very large layers, in multiple myeloma, the presence of calcification in the vessels might really be expected to be more common than reported.

The clavicles seem to be affected with unusual frequency, and the roentgen ray is making it evident that one may speak of the disease as myelomatous even when it is very diffuse. This is well illustrated by the present case, in which it was difficult, if not impossible, to deliver any separate tumor mass completely. Yet as shown by the roentgenogram of the sternum, innumerable distinct tumors were present, making the photograph of the sternum look as though it contained innumerable bubbles.

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6. Turner, W. G.: Myeloma of the Vertebrae, J. Orth. & Surg. **3**: 698 (Dec.) 1921.

7. Christian, H. A.: A Multplie Myeloma, J. Exper. Med. **9**, 1907.

8. Morse, P. F.: Perioxidase Reaction in Three Cases of Multiple Myeloma of Bones, with Remarks Concerning the Nosological Position of These Tumors, J. Cancer Research **5**:345 (Oct.) 1920.

9. Meyer, A. W., and Swain, R. E.: Side-Lights on Multiple Myeloma, Am. J. M. Sc. **156**: 329 (Sept.) 1918.

Both this case and the one previously reported (Meyer and Swain) presented a history of syphilis and arthritis, and showed numerous fractures, fairly marked scleroses, calcareous deposits and evidences of periostitis in the form of roughenings of the external surface of a number of bones. The spleen was very small in the present case, weighing only 104 gm., and the uniqueness of the case lay in the peculiar deposits in many of the articular cartilages and the extensive urate deposits in the subcutaneous tissues and in some of the injured tendons.

REPORT OF CASE

A cigar maker and wood carver, aged 68, died of bronchopneumonia. In the clinical diagnosis, the presence of arteriosclerosis, bronchial asthma and chronic hypertrophic arthritis were noted. It probably is significant that 3 per cent. of albumin was present in the urine, and possibly also that the patient stated that he had had "sciatica" all over his body for years. His chief complaint on admission was shortness of breath on exertion, the duration of which he could not recall. The arthritis deformans was said to have begun fourteen years before.

COMMENT

In view of this fact, this period may also have been the duration of the myelomatous condition, especially so since the patient stated that he had "sciatica all over" for years. Multiple myeloma is assumed to run a rapid course, the usual duration, according to Nonne [10] (1921) being only one and one-half to two years and the longest duration on record being that of Graves' case, with a history of six years. According to Hirschfeld [11] (1920), the case of Kahler had a duration of eight years. Since the deformities in the hands, which were responsible for the diagnosis of arthritis deformans in this case, very evidently were due to the myelomatous condition, a long duration would seem very probable.

In view of the fact that the deforming deposits in the subcutaneous tissues of the fingers were urates, it does not seem unlikely that these deposits had their origin in the extensive destruction of tissues necessarily accompanying multiple myeloma. Although it should be remembered in this connection that, in the case of Beck and McCleary, tophi were present in the ears, and a diagnosis of chronic gout was made. One cannot exclude the coexistence of gout in the present case, although such a diagnosis was not established clinically.

On inspection of the cadaver before dissection, large pigmented areas, evidently scars, in the anterior tibial regions were noted. A pronounced anterior curvature was present in the right tibia. This the history recorded as probably being congenital. Two nodular irregularities in the right clavicle suggested

10. Nonne, M.: Beitrag zur Klinik der Myelom Erkrankung, Arch. f. Dermat. u. Syph. **132**, 1921.

11. Hirschfeld, Hans: Das Myelom Spezielle Pathologie und Therapie innere Krankheiten, Vol. 8, Berlin, Wien, Kraus-Brugsch, 1920.

that the latter had been fractured twice, and a similar nodule in the left clavicle suggested that it also had been fractured. The most striking thing about the cadaver was the marked deformity of the hands, shown in Figure 1. The appearance of these deformities seemed to confirm the presence of arthritis deformans recorded in the history.

The entire cadaver looked decidedly senile and rather emaciated. Because of its apparent age and the fact that almost two years had elapsed since the patient died, no special significance was, at first, attached to the fact that all the ribs had been fractured in transportation by external pressures on the ventral surface of the thorax and that the left posterior parietal region of

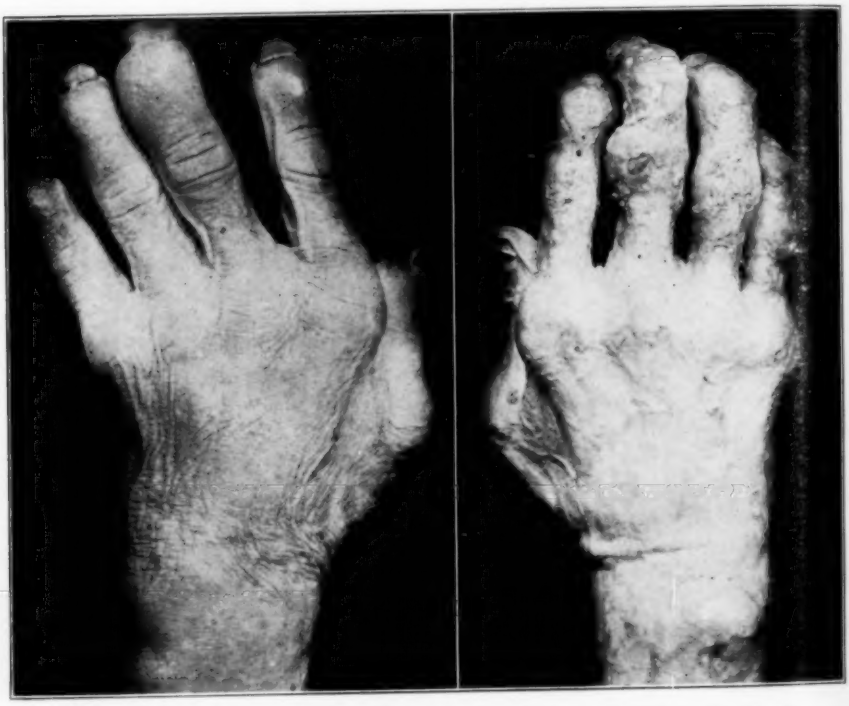

Fig. 1.—*A*, dorsal view of the intact left hand; *B*, dorsal view of the right hand with the skin removed.

the skull was depressed. These things might have been due to postmortem injury. It seemed strange, however, that the ribs were so extremely pliable and that the sternum and calvarium yielded very easily to pressure. But since senile absorption not infrequently is very pronounced in these bones, this lack of usual resistance received no further attention, as the clinical history was not known at that time. It is significant in this connection that tenderness to thoracic pressure had been noted in the clinical history.

As soon as the scalp had been dissected, it was found that the entire calvarium was mottled, as shown in Figure 2, and that only a very thin plate of compacta remained in most of the affected regions. Closer examination showed that

the thin layers of bone overlying the darkened areas beneath were largely decalcified and that slight pressure caused them to yield.

Since the appearance of the calvarium was characteristic, and particularly since we had previously met with a case of multiple myeloma in the dissecting room, this disease naturally came to mind although no mention had been made of it in the clinical history. The surmise that this was a case of myeloma was confirmed by a reexamination of the places of fracture in the clavicles, and particularly by the extraordinary condition of the ribs and sternum. Further examination of the hands also revealed the fact that some of the nodules on the fingers were superficial and movable, and hence were deposits

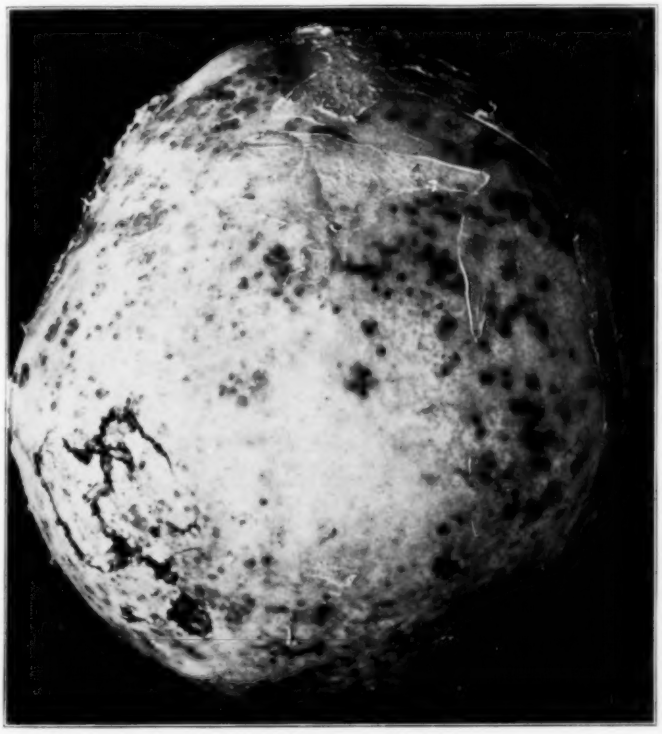

Fig. 2.—Calvarium, showing the numerous tumors.

instead of osseous deformities due to arthritic changes. This inference was confirmed by further dissection; for even the large deposit on the dorsolateral surface of the medial phalanx of the third finger of the right hand could be easily removed from the underlying tendons and periosteum without damaging them. This was true also of the pronounced deposits responsible for the major part of the deformity at the distal interphalangeal joint of the same finger of the left hand.

The appearance of the larger calcium deposit is shown in section in Figure 3. This deposit measured approximately 2.5 by 1.5 by 1 cm. All these deposits were quite friable and largely devoid of tissue, and offered no special resistance

to the edge of the knife. Their texture and appearance suggested calcium. Tophi were not present, and nothing else directed attention to the possible existence of gout.

The gross examination of the calvarium showed that it was impossible to enucleate any of the tumors because they were insufficiently well delimited and too friable. This was quite in contrast to the case reported by Meyer and Swain. The tumors in the latter case were definitely delimited and could easily be removed intact after stripping of the periosteum.

As Figure 2 shows, most of the areas in which the myelomas had almost penetrated the external table of the calvarium were relatively small, ranging from pin-point size to approximately 1 cm. in diameter. However, in the right frontal region there was one much larger area, measuring 3.5 cm. in diameter. Here, the tumor was overlaid only by a thin plate of largely decalcified compacta. The destruction of bone seems to have been particularly complete in this area. The myelomas were so generally distributed throughout the calvarium that it was difficult to remove any of them without breaking the skull, and on

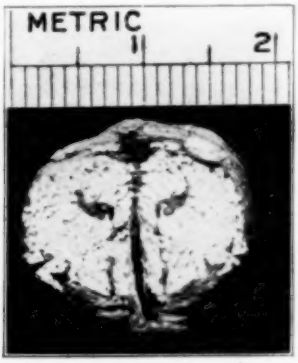

Fig. 3.—Large deposit from the dorsolateral interphalangeal region of the third finger of the right hand, in cross section; ×2.

attempting to detach the dura mater, it was found impossible to do so without running the risk of seriously damaging the calvarium or the base of the skull. Yet none of the tumor areas projected beyond the level of the calvarium either externally or internally. The dura was tightly adherent and somewhat thickened, but this was not the case with the pericranium, although it, too, seemed more closely adherent than usual. An inspection of the interior of the rest of the cranial cavity, especially of the base of the skull, showed that this was similarly, although not quite so generally, affected. The mandible showed no evidence of lesions on external inspection of the face before dissection.

The appearance of the exterior of the calvarium suggested that the tumors probably were disseminated throughout the entire diploë, and this surmise was confirmed by a roentgenogram, reproduced in Figure 4. As inspection shows, there was no area of the entire calvarium which was not affected by a multitude of tumors, many of which do not show in the roentgenogram because of the normal curvature of the calvarium. A similar condition existed in the sternum (Fig. 5) and also in all the ribs, which were affected throughout their entire length. With the exception of the first and second ribs, the entire shafts were practically destroyed, nothing but a very thin plate of decalcified bone of the thickness of paper remaining. Several score of healed fractures, some of them accompanied by considerable displacement, were present in the ribs,

and the heads of many of them were ankylosed to the vertebrae, which were practically unaffected, with the exception of the first thoracic and the second and fourth lumbar, which were slightly affected. The marked bone absorption accompanying the general tumor formation was responsible for the decided weakness of the ribs noticed during the inspection of the intact cadaver. The condition of the ribs was in marked contrast to that found in the former case, in which all the large tumors in the ribs were definitely circumscribed and had

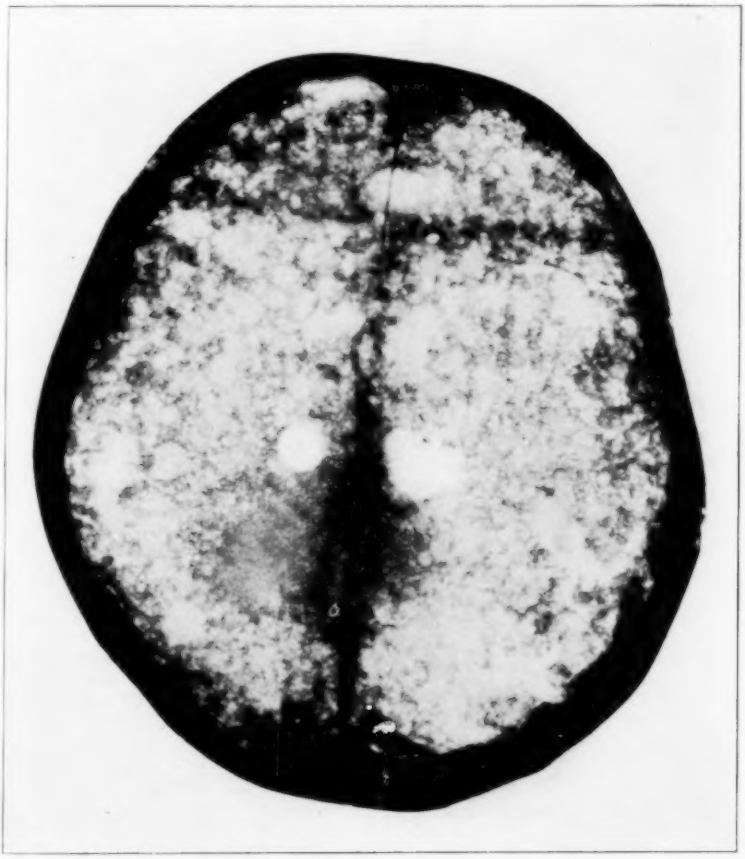

Fig. 4.—Calvarium showing innumerable tumors.

completely severed the affected bones. Moreover, in this case there was practically no decalcification beyond the immediate area of absorption.

The chief characteristic of the myelomatous condition in this second cadaver was the general dissemination of tumors throughout the ribs, sternum, skull and mandible. The rami of the latter and the greater portion of the corpora were completely affected with tumors, only a thin shell of compacta remaining in the region of the rami and angles, as shown in Figure 6. A roentgenogram

of the base of the skull (Figure 7) showed that it was affected as seriously as the calvarium, not even the zygomata or condyles being free of tumors.

Roentgenograms of the left upper extremity show that all of the scapula except the central portion of the body was almost as completely filled with tumors as the calvarium. The absence of tumors in the midportion of the scapula probably was due to the thinness of the spongiosa. The head and the tuberosities and the proximal portion of the surgical neck of the left humerus were practically unaffected, and little evidence of tumor formation was present in the condyles and epicondyles. The rest of the diaphysis showed the presence of

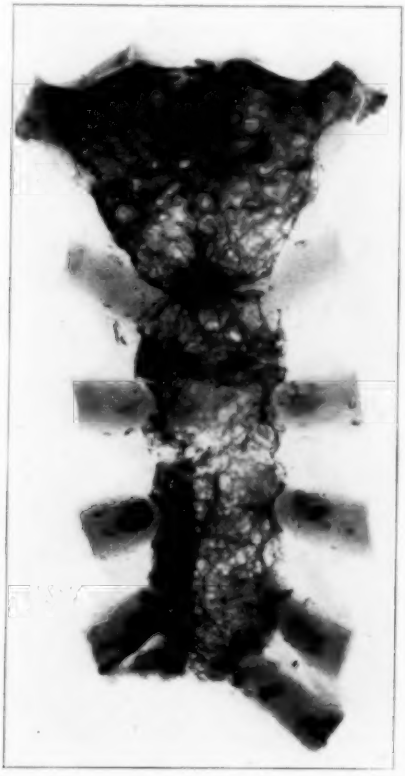

Fig. 5.—Sternum, showing innumerable tumors.

large numbers of tumors. They lay in contact with each other throughout the entire extent of the medulla.

The left clavicle contained a callus, evidently due to fracture, about 3.5 cm. from its distal extremity, and numerous tumors throughout its shaft. Only a thin shell of compacta remained in the greater portion of the distal two thirds of the bone.

The radius and ulna, particularly the latter, contained only slight evidences of the presence of tumors, except for the fact that the distal extremity of the ulna in the region of the styloid process seemed to have been affected. The

carpal bones of the right hand were practically normal, but the first, second, fourth and fifth metacarpals contained evidences of tumor formation. The phalanges of the thumb were free, but the middle and terminal phalanges of the second and third fingers were markedly affected and ankylosed.

The left ilium and ischium were much affected, though containing no single large tumor area such as that in the right ilium. The left femur was but slightly affected in its upper half with the exception of the head and tuberosity. The patella was clear, and the same thing seemed to be true of the tibia, but the diaphysis of the fibula apparently was affected slightly throughout its entire extent.

With the exception of the internal cuneiform, the bones of the left foot, the first metatarsal and the phalanges seemed to be unaffected, but the entire

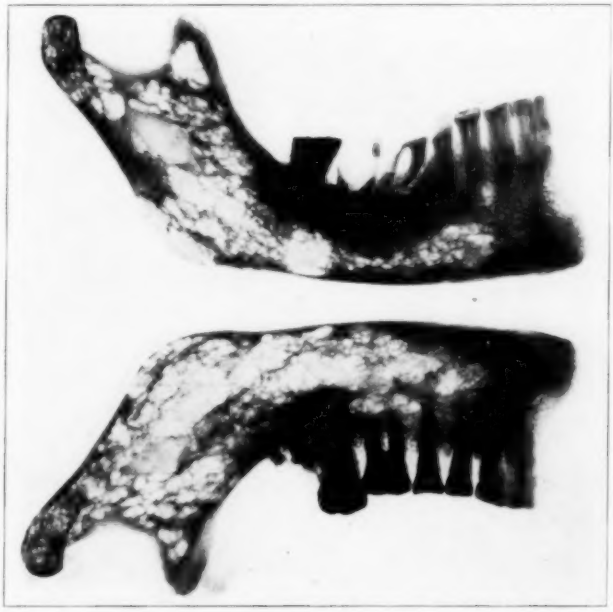

Fig. 6.—Mandible showing innumerable tumors, except in the mental region.

right ilium, with the exception of the thin area in the middle, was extensively involved. A large oval area about 7 by 6 cm. in size in the vicinity of the anterior superior spine formed one large tumor which was elevated slightly and irregularly above the normal surface though still covered by rough bone. A greater portion of the tuberosities of the ischium seemed unaffected.

The head, neck and tuberosities of the right femur and also the distal fifth of its diaphysis seemed to be wholly unaffected, but the rest of the diaphysis contained disseminated tumors. The lower half of the condyles of the tibia contained no recognizable tumors, and the rest of the bone contained only scattered ones. The entire diaphysis of the right fibula was greatly rarefied and contained scattered indications of circumscribed tumors. The roetngenograms suggest that the marrow of the entire bone was affected and that bone absorption was quite general. All the toes and the heads of the first

and fourth metatarsals contained evidences of tumors, but the rest of the right foot, with the exception of the lateral margin of the cuboid, seemed to be unaffected.

The condition of the right scapula was similar to that of the left, except that the inferior extremity had been fractured over an area of about 2 cm. This fragment, although displaced laterally about 4 mm., had completely united with the body. Callus formation was but slight, and only a small area of the

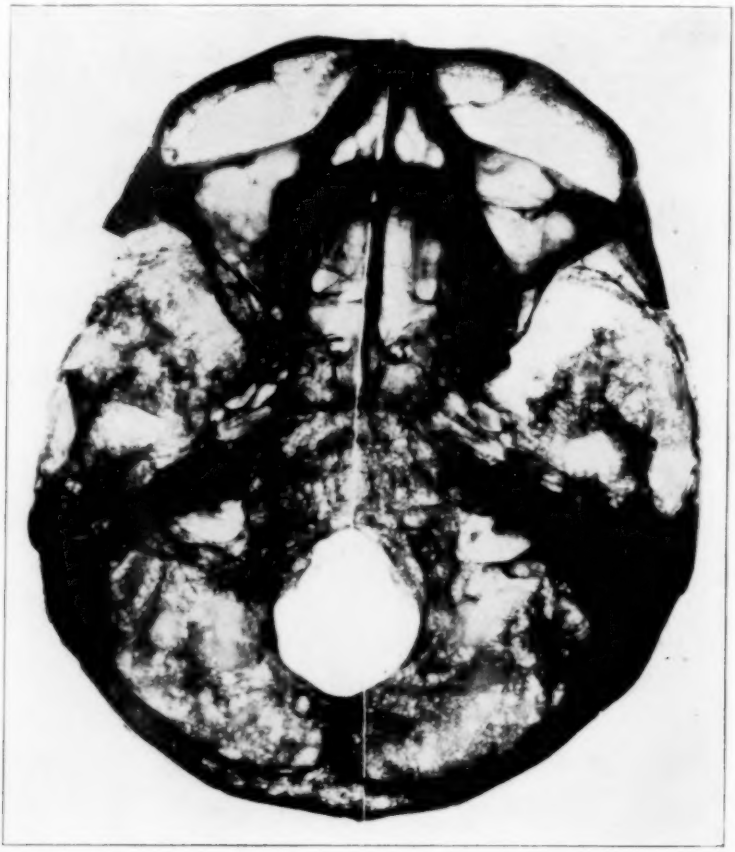

Fig. 7.—Base of the skull indicating extensive bone absorption also in this region.

central portion of the body was free from tumors, as judged by the roentgenogram. The superior, medial and lateral regions were entirely interspersed with tumors, the largest of which measured about 6 mm. Most of the spine and head, and the acromiom and coracoid processes seemed free of tumors.

Aside from the marked deformity due to displacement and thickening of the proximal extremity of the right clavicle, the most noticeable thing in the roentgenogram of this bone was the extensive destruction of the shaft.

The condition of the right humerus was quite comparable to that of the left, the head and anatomic neck and the condyles and epicondyles containing no tumors.

The radius seemed only slightly affected in the greater portion of the diaphysis. The largest tumor, which measured only about 4 mm. in diameter, was located distally to the radial tuberosity. The conditions of the diaphyses of the right ulna and fibula were similar to those existing on the left side.

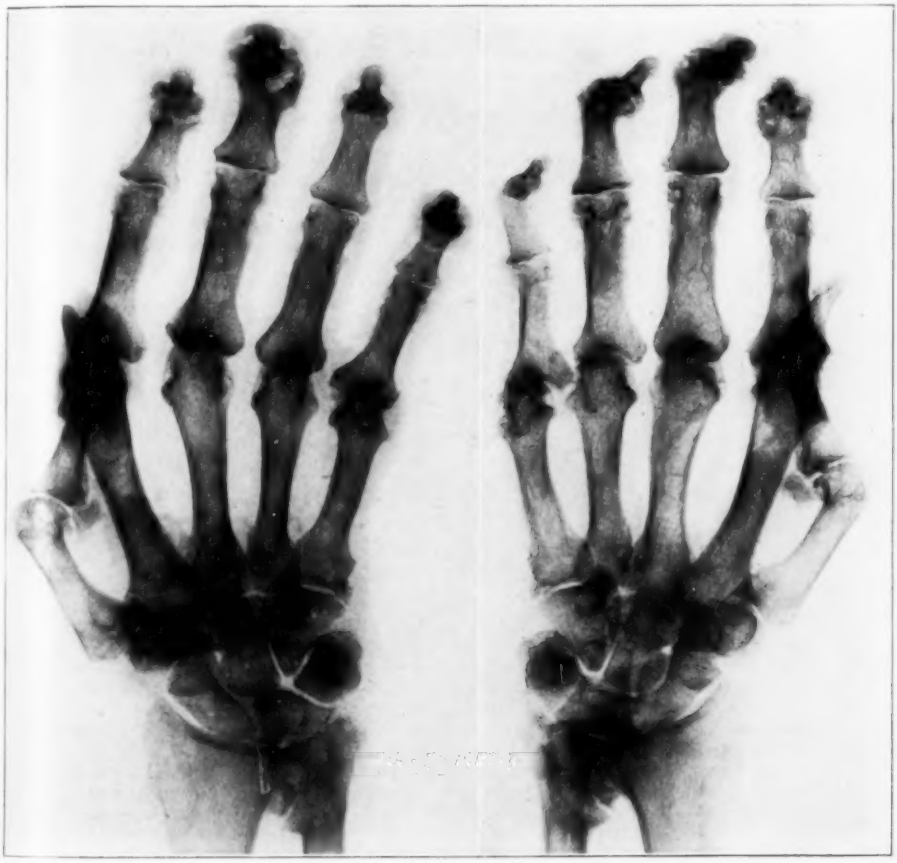

Fig. 8.—*A*, left hand and wrist, showing the peculiar exostoses at the radio-ulnar articulation; *B*, right hand, showing identical conditions.

The fact that the osseous deformities on the distal extremities of the radius and ulna in the left arm were repeated almost exactly in the right is of particular interest. This duplication was practically identical even to the presence of the tumors in the styloid process of the ulna.

The condition of the metacarpals and phalanges was similar to that noted in the left hand.

A marked right scoliosis was present in the region of the second to sixth dorsal vertebrae. This was uncompensated for in the lumbar region, and careful examination of the entire spine failed to reveal any cause for it. However, since two old fractures were present in the right clavicle, it is not improbable that this scoliosis was the result of the posture assumed by the patient in an attempt to protect the more severely injured side.

Two small defects were present in the capsule of the left shoulder joint. Both were slitlike, the larger measuring about 1 cm. in length and 3.5 mm. in breadth, and both being located along the dorsal border of the tendon of the supraspinatus. The subcromial portion of the coraco-acromial ligament was worn, as was the entire outer surface of the upper portion of the articular capsule. The subdeltoid bursa was entirely intact, however, and not especially enlarged. The dorsal margin of the intra-capsular portion of the tendon of the long head of the biceps was frayed, but the articular cartilages of the shoulder joint were quite normal.

The capsule of the right shoulder joint was roughened and frayed, and the lateral border of the coraco-acromial ligament was worn to a sharp edge and somewhat frayed. This is particularly interesting since this ligament in the other arm still was continuous with the fibrous expansion which extended to its lateral margin from the coraco-brachialis and long head of the biceps.

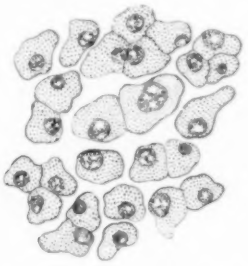

Fig. 9.—A group of typical tumor cells.

The tendon of the long head of the latter showed some calcification, and this is also true of the synovial villi in the interior of the joint. Calcium deposits were present also in the anterior portion of the capsule of the right elbow joint, in which the capitellum and the head of the radius had undergone changes similar to those present in the left arm. In brief, the conditions in the wrist and hand of this arm were similar to those in the left, even to the destruction of and deposit in the tendon of the extensor carpi ulnaris.

Numerous small calcific nodules were present, especially in the lateral portion of the capsule at the elbow joint, and almost the entire capitellum and the head of the radius were polished. Slight lipping was present throughout this joint, and the styloid process and head of the ulna, together with the corresponding articular surfaces on the distal extremity of the radius, were greatly deformed. The fibrocartilage on the ulna was completely destroyed and the medial portion of its distal extremity was formed by an osseous articular surface in the form of a trochlea, with a deep groove which received a markedly prominent and roughened bony ridge on the right radius, shown in Figure 8 *B*. An almost identical condition in the left hand is shown in Figure 8 *A*.

The articular cartilage of many of the carpals, metacarpals and phalanges were slightly or extensively eroded, and the middle and distal phalanges of the third finger almost firmly ankylosed. But the most interesting thing in this entire upper extremity was the presence of deposits in many of the articular cartilages. In the left hand, as in the right, these deposits were present not

only in all ankylosed articulations, but also in most others. Hence, it is not surprising that there was considerable erosion of the articular cartilages with but slight para-articular bony reaction. It is rather difficult to account for the marked distortion of the fingers, except for that in the terminal phalanges, on the basis of bony change.

Similar deposits in the cartilages accompanied by roughening and polishing were present in many articulations of the feet although the tibiotarsal articulations were quite normal. The deposit was most pronounced in the articular cartilages on the medial portions of the feet; that is, in the regions of greatest strain. Strangely enough, no urates were found in the cartilages examined (Cajori).

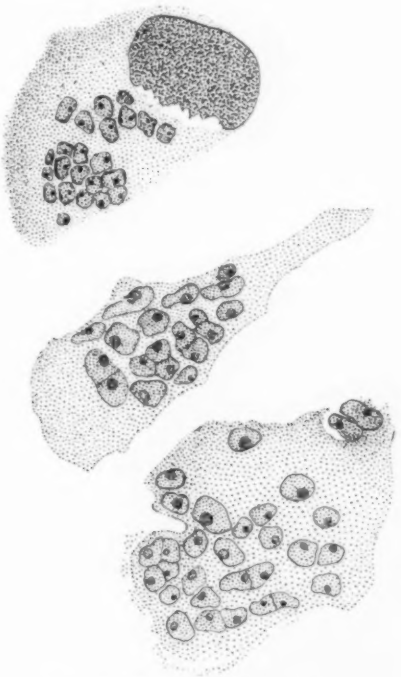

Fig. 10.—A group of osteoclasts.

The deposits were not limited to the joint capsules, to the articular surfaces of some of the bones or to the subcutaneous tissues. They were found also in some of the deep flexor and the common extensor tendons of the fingers. However, they did not unite these tendons to the underlying bone, although some of the tendons were considerably thickened in the region of the deposits. That trauma probably was a factor determining the location of these tendon deposits is suggested, not only by their location in this case, but also by the fact that the worn tendon of the extensor carpi ulnaris, which was partly destroyed by friction through movement on the roughened, large exostosis in the region of the styloid process of the ulna, also contained deposits. Although slight evidences of wear were present in the right hip joint, similar deposits were absent here and also in the right knee joint, except that some of the synovial villi in this joint contained them.

The deposits in the superficial fascia were located in regions exposed to trauma. Except for those located on the fingers and in the tendons, they were small, some being barely visible to the unaided eye. It was particularly interesting that small deposits were found in the subcutaneous and subfascial bursae in the olecranal and in the prepatellar regions. Since it is but rarely that superimposed subcutaneous bursae are found in the olecranal region, it is more than likely that these elbows were subjected to more than ordinary friction. Both subcutaneous or superficial bursae of the olecranon were larger than usual, this being particularly true of the left one. Both subfascial or deep bursae were small, measuring only about 7 mm. across, but the walls of both, as well as those of the subcutaneous bursae, did not suggest the existence of a former infection. I do not know whether slight trauma or friction may have been a factor in determining the location of these subcutaneous deposits, but their location necessarily suggests this. Only a few very small superficial deposits were noticed in the region of the feet, but these also were found in areas exposed to injury.

There was an entire absence of metastases in this, as in the previous case. The local calcium deposits also were in marked contrast both in location and in extent to those in the previous case. There was nothing in the viscera to attract special attention. The lungs, except for minute deposits which gave the cut surface a granular feeling, seemed quite normal. The spleen was decidedly below normal in weight. The aorta and all the great central vessels were in good condition, but the radial arteries were extremely sclerotic and calcified. The same was true of the vertebrals and the internal carotids in the more distal regions. The coronary arteries also were somewhat sclerotic as were the bicuspid and tricuspid valves. Nevertheless, these areas of sclerosis, as well as those in the arteries, would not have attracted attention by themselves. Although pronounced, they were not more so than those often found after death from causes unassociated with myelomata, nor were they so extensive.

Microscopic sections of portions of the tumors removed from the temporal region, the ribs and the ilium showed an entire absence of encapsulation. In many of the areas surrounding these tumors, there was so little connective tissue that one had to look carefully for it. This finding agrees with the fact that it was impossible to remove any of these tumors in their entirety as in the previous case. Indeed, considerable areas of these tumors seemed wholly free from stroma of any kind, the prevailing type of cell suggesting premyelocytes. Not uncommonly, these cells were arranged in cords about a vein, thus roughly simulating a liver lobule.

Although the preservation of these tumors was not adequate to permit a careful cytologic examination, it, nevertheless, was sufficiently good to reveal clearly the fact that there was uniformity in the size and character of the tumor cells. Most of these were from 10 to 12 microns in diameter, with a slightly granular cytoplasm and an eccentrically placed vesicular nucleus, as shown in Figure 9. In many of these nuclei a nucleolus was evident, but in others the chromatin was formed into small granules.

As reported also by other investigators, small, less well-preserved areas were scattered throughout the sections of these tumors. A careful search was made for different types of cells, but none were encountered, except that osteoclasts were present at the periphery of the tumors from the ribs and sternum and were also contained in sections from the large tumor-area in the right ilium. They were quite usual in type, as shown in Figure 10, and were found only at the periphery of the tumors from the ribs because the midportions of these tumors contained no osseous remnants.

The Haversian canals in the surrounding bone were in a condition quite similar to that found in the case previously reported except that there was an absence of an internal bounding layer of cells osteoblastic in character. No matter how wide these canals were, or how great or how irregular the bony

destruction, none (of those examined) contained osteoclasts. The latter were confined largely to the periphery of bony trabeculae and to spicules of bone which lay isolated in the cellular masses of the tumor.

No periosteal reaction was present where the tumors had perforated the bone in the temporal region. Yet the body contained scores of fractures which had healed without a great deal of displacement or an excessive formation of callus. Slight deposits of a brownish pigment were noticed, particularly in the affected regions from the temporal bone, small areas of which did not seem to show the presence of tumor cells. They contained shadow forms of fat cells instead. In other areas, the adipose marrow contained scattered tumor cells throughout its entire extent. This seems particularly interesting in view of the fact that the extremities of the long bones, where red marrow is retained longer, were not at all, or but very slightly, affected. The diaphyses of these bones, on the other hand, were markedly affected, in spite of the fact that the body was that of an individual 63 years of age. Hence, one either must assume that the myelomatous condition had existed for decades or that it encountered no difficulty in extending into or in beginning in fatty marrow. It is true, nevertheless, that the red marrow was affected more generally than the yellow. This is well exemplified by the condition of the calvarium, and by that of the entire skull, the ribs, the sternum and such long bones as the phalanges, the metacarpals and metatarsals and such short bones as the carpals and tarsals.

Microscopic examination of the large deposit over the distal interphalangeal articulation of the middle finger of the left hand revealed large areas many of which were composed exclusively of deposit. Some of these contained considerable quantities of yellowish pigment which, strangely enough, gave the impression of being diffuse in some areas. These deposits were transversed by many coarse trabeculae of fibrous connective tissue, some portions of which were decidedly infiltrated with large lymphocytes, most of which contained a somewhat more extended margin of cytoplasm. Not infrequently these areas of infiltration were located near blood vessels. Although the section examined contains a portion of the common extensor tendon, the latter did not contain deposit throughout its entire extent. A small portion of it contained a large mass near one side of which smaller deposits were found. A small portion of bone, apparently a portion of an exostosis, also showed the presence of some osteoclasts and considerable destruction. Aside from being very vascular, the subcutaneous tissues over this area showed nothing peculiar.

There was an entire absence in this skeleton, of anything that could be referred to as an exostoses except on the distal extremities of the radii and ulnae as shown in the roentgenograms of the hands.

Both coxal bones were decidedly massive with markedly roughened surfaces, especially over the ilium, due probably to reactions evoked in the periosteum. This seems the most likely explanation for the presence of the roughening since it was most marked in the regions where the tumors came nearest to the surface in these bones. It is interesting that no such roughening was present on any of the ribs, in the sternum or on the skull. Yet over the entire external surface of these bones, there were numerous small areas in which the tumors came very near to penetrating the compacta.

The roughening of the surfaces of these bones was indeed very simliar to that present in the right tibia, the periosteum of which was somewhat adherent. The vessels were tortuous. Whether or not the marked anterior curvature of this tibia really was congenital, as suggested in the protocol, is open to doubt. The entire appearance of the surface of the bone suggests that it was syphilitic, although the curvature was not such as is regarded as typical in this disease. The extreme vascularity of the bone as judged by the many large vessels that perforate the diaphysis on all sides is as curious as the site of considerable ossification at the place of insertion of the popliteus.

CALCIUM AND PHOSPHORUS CONTENT OF THE TISSUES

Unusual conditions of mineral metabolism undoubtedly prevail during multiple myeloma. They are a result of the extensive lesions in osseous tissue characterized by the replacement of bone by tumor masses.

The attention of investigators has been attracted by the way in which the body disposes of the large amounts of calcium liberated from the bones. That a large part of it is excreted by way of the kidneys and intestines is clearly indicated by the observations of Williams [12] (1910-1911) and Blatherwick [13] (1916). So great was the loss of calcium in the case studied by the latter, that the daily administration of 1.5 gm. of calcium oxid was insufficient to secure a positive calcium balance.

Analysis of various tissues from cases of multiple myeloma indicates that frequently there is an infiltration of calcium salts in some parts of

Calcium and Phosphoric Acid Content of Tissues

Source of Specimen	Ash, %	CaO, %	P_2O_5, %	CaO, % of Ash	P_2O_5, % of Ash	Ca, %	PO_4 %	10 Ca : 6 PO_4 (400:570)
Ribs	31.46	15.84	12.65	50.35	40.17	35.98	53.71	400:597
Skull	59.77	32.18	24.93	53.85	41.71	38.48	55.76	400:580
Femur	57.01	30.96	22.98	54.25	40.27	38.77	53.84	400:555
Femur	54.62	29.52	22.19	54.06	40.63	38.63	54.32	400:563
Rib tumors	5.78	1.51	2.59	26.02	44.87	.....	.....	.....
Finger deposits	15.41	2.77	1.40	18.00	9.09	.....	.....	.....
Trachea	6.21	1.06	0.47	17.10	7.68	.....	.....	.....
Striped muscle	3.79	0.40	0.76	10.62	20.09	.....	.....	.....
Liver	4.56	0.49	0.74	10.89	16.39	.....	.....	.....
Lungs	5.00	0.25	0.96	5.18	19.28	.....	.....	.....
Spleen	5.91	0.37	3.30	6.27	5.09	.....	.....	.....

the body. Bender [14] (1902) reports finding calcium deposits in the lungs, liver and lymph glands and in connective tissue. Tschistovitsch and Kolessnikoff [15] (1909) analyzed several tissues from a case of myeloma and found an abnormally high ash content of the lungs, liver and kidney. In the case reported by Meyer and Swain (1918), the latter found that the percentage of calcium in the large deposits in the parietal pleura was 35.13. There also were excessive amounts of cal-

12. Williams, O. T., and Evans, E. R.: A Case of Multiple Myeloma with Some Observations on the Nature of the "Bence-Jones" Protein Found in the Urine, with a Pathological Report on This and Another Case by E. Glynn, Lancet **2**, 1910.

13. Blatherwick, N. R.: Calcium and Bence-Jones Protein Excretion in Multplie Myeloma, Am. J. M. Sc. **151**:432 (March) 1916.

14. Bender: Ueber ein periostales Rundzellensarcom in ein Myelom mit Kalkmetastasen, Deutsch. Ztschr. f. Chir. **63**:370, 1902.

15. Tschistovitsch, T., and Kolessnikoff, Helene: Multiples diffuses Myelom (Myelomatsis ossium) mit reichlichen Kalkmetastasen in die Lungen und andere Organe. Virchow's Arch. f. path. anat. **197**: 112-135, 1909.

cium in the muscles examined but a very low content in the bones. This was especially true of the bones in which there were extensive tumor lesions.

I analyzed a number of specimens of bones and other tissues from the case of multiple myeloma described in the present paper (Meyer). The samples of the ribs and skull were filled with innumerable tumors. For the sake of comparison, we took a section of the distal third of the diaphysis of the femur, that, judging from roentgen-ray examination, seemed to be free from tumors.

Several of the deposits over the distal interphalangeal joints described above were dissected out and analyzed. It also seemed desirable to study the actual tumor masses, sufficient quantities of which were removed from the ribs. In addition, samples of the liver, lungs, spleen, trachea and the quadriceps extensor muscle were examined.

Each specimen was prepared for analysis by dissecting it as completely as possible from adhering tissue. It was then cut into fine pieces and dried at 110 C. to constant weight. The ashing was done in platinum dishes at a dull redness. The ash was dissolved in hydrochloric acid. Calcium was determined by the McCrudden method and phosphoric acid by the usual gravimetric procedure.

The analytic results are given in the accompanying table.

The ribs showed an extremely low ash content as compared with that of the apparently normal femur. Hence, it seems that actual decalcification of the bone, as suggested by gross examination, had taken place. It is rather surprising that a like result was not obtained in the calvarium, where the tumors were very numerous. A portion about 5 cm. in diameter taken from the left parietal region was almost normal in composition.

It will be noted that the ratio of Ca to PO_4 in the bone samples is not far from 400 to 570, the ratio existing in normal bone. Swain (Meyer and Swain, 1918) also found that this ratio had not changed significantly in the myelomatous bones examined by him.

The low ash content of the tumor masses shows how completely the bone was decalcified in some regions. The low mineral content of the finger deposits dispelled the idea that these were composed mainly of lime salts. A few milligrams of the deposit were sufficient to give strongly positive murexid and phosphotungstic acid tests for uric acid. Hence, the deposits were largely made up of salts of uric acid instead of calcium as seemed likely. I found no evidence of extensive deposits of calcium salts in any of the tissues examined, although the ash content of the muscle and liver was somewhat higher than that given by

Albu and Neuberg [16] (1906). The trachea also shows a high calcium content, but these excesses do not account for the large quantity of calcium liberated from the bones.

In view of these findings and the published reports of balance experiments on multiple myeloma, it seems probable that the calcium liberated in the destruction of bone tissue is rapidly and in a large part excreted from the body and, in relatively small amounts only, is deposited in other parts of the body.

16. Albu, A., and Neuberg, C.: Physiologie und Pathologie des Mineralstoffwechsels, Berlin, J. Springer, 1906.

THE HISTOGENESIS AND NATURE OF GAUCHER'S DISEASE *

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AND
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Although one of the rarer pathologic lesions, the primary idiopathic splenomegaly of Gaucher has been the subject of considerable discussion. This has centered more particularly around the cytogenesis of the characteristic large round to oval or polygonal single or multinucleated cells, which comprise the bulk of the splenic tissue and account for the splenic enlargement. Since the original neoplastic conception of the nature of these cells was replaced by that of a hyperplasia, there have grown up two schools, one tracing their origin to the endothelial lining of the venous sinuses, the other to the reticular tissue of the pulp. The former view has been supported by Bovaird, Downes, Wilson, and others; the latter by Schlagenhaufer, Risel, De Jong and Van Heukelom, etc. A few have expressed the opinion that these cells may arise from either source.

Mandelbaum,[1] in 1912, called attention to the fact that up until then no one had shown any transitional stages in the development of these cells, either from the endothelium of the venous sinuses or from the reticular cells of the splenic pulp. Such changes, however, he stated, could be demonstrated in the lymph nodes where the process was not so far advanced, and here a reticular origin was suggested. In later papers,[2] appearing in 1916 and 1919, he expanded this idea, and considered it evident that a similar development occurred in the spleen; and, since there was a free communication of the sinuses with the pulp, it seemed possible that most of the free Gaucher cells within the sinuses had come from the surrounding pulp and were derivatives of the reticulum. He stated, however, that in all cases which he had examined, the process in the spleen was too far advanced to permit of exact determination as in the lymph nodes, and that there was no positive evidence

* From the Pathological Institute of McGill University and the Royal Victoria Hospital.

1. Mandelbaum, F. S.: A Contribution to the Pathology of Primary Splenomegaly (Gaucher Type), with the Report of an Autopsy on a Male Child Four and One Half Years of Age, J. Exper. Med. **16**:797, 1912.

2. Mandlebaum, F. S., and Downey, Hal: Histopathology and Biology of Gaucher's Disease (Large-Cell Splenomegaly), Folia hematol. **20**:139, Arch. **3**, 1916. Mandlebaum, F. S.: Two Cases of Gaucher's Disease in Adults. A Study of the Histopathology, Biology and Chemical Findings, Am. J. M. Sc. **147**:366 (March) 1919.

in the spleen that the endothelium of the sinuses did not take part in the formation of large cells, and that the possible origin from this source could not be denied.

The extraordinary opportunity for throwing light on this problem that would be offered by the examination of a spleen in which the lesion was not far advanced has, therefore, been generally recognized for some time. Such an organ was recently removed at the Royal Victoria Hospital. Both clinical history and pathologic examination indicated that the process was comparatively early. Consequently, at the suggestion and under the supervision of Professor Oertel, we carried on detailed histologic studies of the tissue. The results have been very instructive and give us a much clearer conception of this unique condition than has previously existed.

REPORT OF CASE

History.—S. C., a Hebrew girl, aged 5 years, has always been apparently a comparatively healthy child. Two years before, she had scarlet fever, and at that time her physician noted that the spleen was abnormally large. It did not decrease in size on recovery. About a year later, she was examined again, and it was found that the spleen had enlarged quite rapidly since her illness. Subsequent examination, a few days prior to admission, showed that progressive enlargement had occurred. At this time, the liver extended three finger breadths below the costal margin; there was a somewhat sallow color with malar flush, and a fluctuating pulse was present. The child had felt perfectly well, never complained, played with the other children and enjoyed a good appetite. The condition was considered surgical and the patient was admitted to the Royal Victoria Hospital, service of Dr. George E. Armstrong, April 11, 1922.

The family history was negative. The father and mother were well. There was a son older and a daughter younger than the patient, both apparently normal and healthy.

Examination.—The patient was well developed and well nourished and apparently of stated age. The contour of the body was normal except for a somewhat enlarged pendulous abdomen, which was moderately tense. The skin was sallow, and there was no appreciable darkening of the skin of the face and hands. The mucous membranes appeared normal. There was no cyanosis, edema or ascites. The pupils were equal and reacted actively to light and in accommodation. There was no wedge-shaped thickening of the conjunctivae. The temperature was 98 F.; pulse, 110; respiration, 20.

Examination of the lymphatic system revealed no pathologic enlargement of the glands. The respiratory system was negative. The pulse was somewhat irregular, rapid (110) and of good volume and fair tension. The heart showed slight enlargement to the left. There were no adventitious sounds. The blood picture showed leukopenia with relative lymphocytosis, but was otherwise normal. The abdomen was large, somewhat firm and pot-shaped. On palpation, there was no muscular rigidity, but a certain resistance. The liver extended 3 finger breadths below the costal margin. It was not tender, and the surface and edge were smooth. The spleen was easily palpated and extended well below the umbilicus on the left side, passing to the right of the midline at its lower pole. Here, a definite notch could be felt. There was no evidence of any other palpable mass in the abdominal cavity, or any localized area of tenderness. The nervous, locomotor-integumentary and genito-urinary systems were negative.

Operation.—Splenectomy was performed, April 13, by Dr. Armstrong. The patient had an uneventful recovery, and was discharged, April 28, showing improvement in color, and a suggestion of diminution in size of the liver.

General Pathologic Anatomy and Histology.—The spleen showed a uniform enlargement and preserved the usual shape, except for numerous notches. It weighed 345 gm. and measured 16 by 9 by 4.5 cm. It appeared solid, but not firm in the sense of a fibrosis. The capsule was thin and smooth; wrinkled on bending the organ, and stripped with ease. Scattered over the surface were numerous pin-point gelatinous darker spots. On section, the cut surface appeared pale brick red and pulpy, and dripped a little blood. The trabeculae were not prominent, and there was no evidence of fibrosis. Scattered throughout the cut surface were small round discrete, pin-head sized points, pale and gelatinous, which resembled amyloid malpighian corpuscles. The splenic vessels could not be made out.

Sections, cut very thin and stained by the routine hematoxylineosin method, were first examined for general information, such as histologic arrangement, etc. The capsule showed nothing abnormal, and there was no evidence of any thickening. The trabeculae were seen springing from the inner side of the capsule in the usual way and dividing the splenic tissue into compartments. Both capsule and trabeculae showed the usual structure, fibrous connective tissue interspersed with a variable amount of smooth muscle cells.

The striking feature, as seen under low magnification, was the almost complete replacement of the pulp by alveolar spaces of various size and shape which contained the typical large, clear cells characteristic of Gaucher's disease. Many of these alveoli were lined by a layer of the Gaucher cells and contained free cells within the lumen. Others contained comparatively few of these cells, but were filled with erythrocytes. While a great many, the majority perhaps, were completely filled by these large cells and appeared as solid masses or cords. Thus, also, neighboring alveoli coalesced and were distorted into varying shapes. Such alveoli, filled or partly filled in varying degrees with large pale-staining cells, dominated the picture and made up by far the greater part of the splenic substance. The small amount of normal splenic pulp which remained was compressed into narrow strands and small triangular masses between these closely packed distended alveoli.

The alveoli of Gaucher cells showed great differences in size and shape (compare examination of serial sections below). Furthermore, their arrangement was most striking. Peripherally, under the capsule, they were for the most part large and loosely approximated, with little interalveolar substance. As one passed inward, however, they became more irregular in size and shape, and interpolated between them was a gradually increasing amount of uninvolved pulp. Finally, one approached irregular larger and smaller districts in which the large alveolar arrangement was in a great measure lost, and the Gaucher cells lay in groups and clusters. These districts of less involved splenic substance varied in size from a merely microscopic area to quite large territories. They were irregularly scattered throughout the bulk of the organ but never approached the capsulated surface. They are not to be confused with the malpighian corpuscles or isolated lymphoid follicles. The former appeared to be reduced in number, their vessels intact but with a swollen and protruding endothelial lining. The arrangement of the alveoli about the corpuscles was likewise peculiar. Instead of the lymphoid mantle forming a sleeve for the artery, it was more often eccentric and one side of the artery was relatively or completely free of lymphoid cells. Here, however, were seen small clusters of Gaucher cells which assumed a more alveolar arrangement as one drew away from the vessel. Some arteries were completely devoid of enveloping lymphoid tissue and were surrounded on all sides by, at first very small, then gradually larger, groups of Gaucher cells, until finally large acini were encountered. No Gaucher cells were found deeply within the corpuscle, but at its periphery occasional single or small clusters of these cells could be seen. The isolated

lymphoid areas with large pale staining so-called germinal centers were numerous. Around them, the arrangement was variable. Often, large alveoli pressed directly against the periphery of the lymphoid tissue; while in other places there were smaller and larger clusters of the Gaucher cells.

The alveolar spaces were inclosed by sinus walls which were composed of a basement membrane of endothelium and a very thin stroma of fibrous tissue. But the condition of the walls varied greatly with the advance of the process. If we commenced with an alveolus in which there was no actual distension of the wall by accumulated cells, it was found that the wall was well lined by endothelial cells. These cells had a faintly acidophilic cytoplasm and nuclei which were elongated and flattened and possessed rounded ends (typically endothelial). They did not tend to bulge into the lumen. Some of these cells showed a considerable variation in structure and staining affinity. The nucleus might stain deeply and the chromatin was then uniformly distributed. In others, the nucleus appeared swollen with the chromatin arranged in vesicular manner. The fibrous stroma of the wall acted as a supporting framework and as an intercellular substance for the endothelial cells. It consisted of very fine fibrils interlaced in various directions. In other, generally larger, alveoli the endothelial cells appeared stretched, compressed, flattened and atrophic; the nuclei were elongated and thinned, and stained deeply. Compared with these were sinuses in which the lining endothelial cells appeared larger than usual. Their cytoplasm was acidophilic (hematoxylin-eosin); their nuclei were swollen, elongated, oval and vesicular, and their chromatin was clumpy and was clearly aggregated to the nuclear membrane. Still others were in places devoid of endothelium, and the denuded fibrous connective tissue cells which were stretched remained clear between the Gaucher cells and the interalveolar capillaries.

About some alveoli, the sinus wall formed a complete circle; while in others, it was incomplete and straits of communication between neighboring alveoli were to be observed. This was particularly the case in the areas described above where the alveoli were smaller and more irregular.

The alveoli were made up for the most part of the typical Gaucher cells. Their number within a sinus varied greatly, from a comparatively few, to those filling the sinus completely. In some alveoli these cells appeared distinct from the endothelial cells of the sinus wall. In others, they were attached immediately to the wall and no normal endothelium was seen. In selected sections, where the process was not too far advanced, the Gaucher cells appeared continuous with endothelial cells of the sinus wall and were definitely attached to them without any line of demarcation. Other areas showed the cells attached to the wall by a pedicle, having a broad base and a thin fibrillar stalk. Some were single, while others were united by processes to other cells which projected into the lumen as irregular masses. Many of the Gaucher cells lay free in the sinuses, singly and in clumps. In many instances, they lined the sinus wall in a single layer; in others, there were several layers in varying degrees conforming to the shape of the sinus. Many were united in syncytial manner, with irregular spaces between them. Finally, there were completely filled sinuses which appeared as solid masses or cords. In many of these, the lining wall which separated the individual sinuses had disappeared, and thus larger cell aggregates were formed.

Blood was present in a considerable number of the sinuses, and more particularly in those which were large, and had a central lumen and a narrow margin of Gaucher cells. The erythrocytes were often closely adherent to these cells, and in those sinuses in which there was a syncytial arrangement, blood cells lay in the small spaces between the Gaucher cells.

Individually, the Gaucher cells varied greatly in size and shape (from 20 to 50 microns and even larger). The shape depended largely on whether the cell was free, in clumps or in large masses. The free cells appeared rounded or spherical, while if compressed in masses the shape became altered, usually

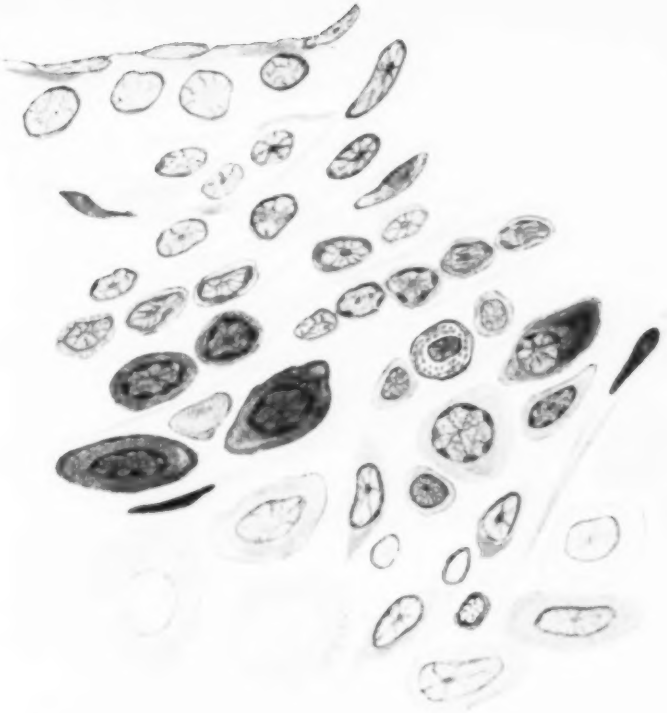

Fig. 1.—Camera lucida drawing of perivascular district, showing stages in differentiation of Gaucher cells.

Fig. 2.—Camera lucida drawing, showing differentiation of endothelium lining a sinus.

polyhedral. In other places, the outline of the cells could not be made out, but blended as a syncytium. Many had branching processes, which might be compared in appearance to the dendrites of nerve cells.

These cells stained with difficulty. Their cytoplasm was acidophilic, pale, swollen, turgid, vesicular and irregularly vacuolated. It had a fibrillated appearance, with very fine fibrils running in all directions, thus forming an irregular meshwork. Many cells appeared to be finely granular. The cytoplasm had a honeycombed appearance, a spongy network in which the paraplasmic fibers appeared to have taken up the stain and inclosed in their meshes a homogeneous, unstained substance. In some cells, particularly in those near

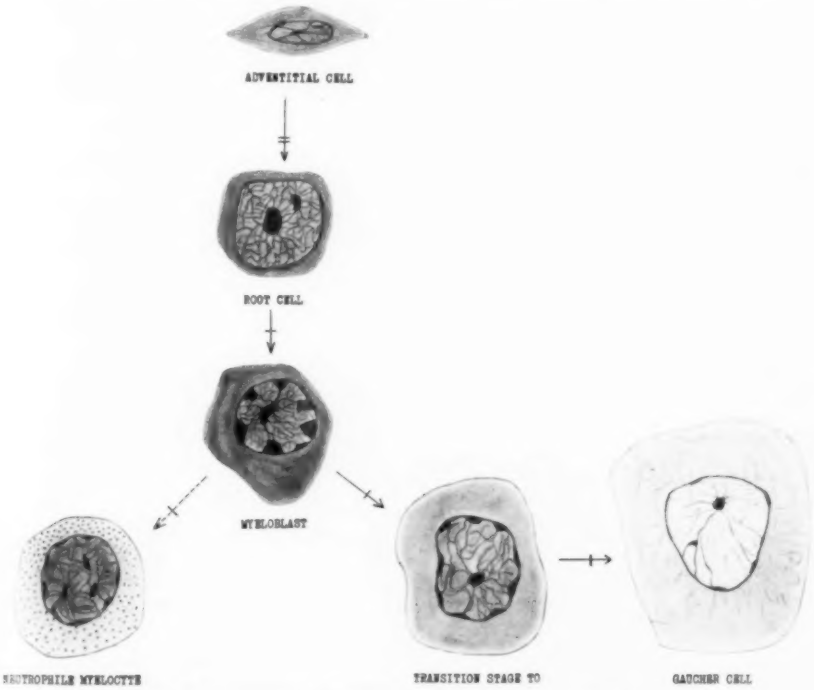

Fig. 3.—Diagrammatic scheme of cytogenesis of Gaucher cell.

the endothelial lining of the sinus, the cytoplasm stained much more deeply. It was acidophilic, with a purple tinge; appeared more homogeneous and more finely granular and exhibited smaller and less irregularly shaped vacuoles. Centrally, the cells were paler, more vacuolated and with indefinite irregular margins. Many of the cells were multinucleated, as many as seven nuclei being seen in a single cell. Frequently, there was only one. The nuclei were small as compared with the size of the cell and varied in position, many being eccentrically placed. They were usually round or oval, but were sometimes distorted, especially in the free cells. The nuclear membrane was prominent, and there was usually one or more nucleoli, or clumps of chromatin material. The majority of the nuclei appeared swollen, turgid and vesicular, with clumps and strands of chromatin material irregularly distributed over a very fine fibrillar

meshwork. In many, the chromatic material tended to be aggregated more densely around the periphery, thus giving the nucleus a darker rim with a paler center. In general, it may be said that the cells in small groups and those which lay at the periphery of large alveoli stained more deeply as regards both their cytoplasm and their nucleus; while the central cells of large alveoli were paler, swollen, washed-out in appearance and more often fused into multinucleated syncytia. Many of these larger cells contained in their cytoplasm a finely granular yellowish pigment.

Cytology and Cytogenesis of the Gaucher Cells.—Frozen sections were prepared from the spleen and the following special staining reactions carried out:

(*a*) For fats by the sudan III and Nile blue reactions. No evidence for the presence of any fatty or lipoid substances could be seen in the Gaucher cells. Unstained sections were examined also with the polarizing microscope, but no anisotropic bodies were made out. This result is in contrast with the findings of Wahl and Richardson,[3] who report anisotropic bodies in many of the large cells in their case, and positive staining reactions for lipoids.

(*b*) For amyloid with methyl-violet and acetic acid, and also with iodin and sulphuric acid. No trace of amyloid degeneration was found.

(*c*) For oxydase by the methods of Schultz and McJunkin-Charlton. The Gaucher cells were negative, while the neutrophilic and eosinophilic granular cells scattered throughout the tissue contained dark blue granules which caused them to stand out prominently.

Sections were examined in series particularly with the view of tracing the boundaries and relations of individual sinuses. It was found that, although they varied greatly in size, nevertheless many of the apparently small sinuses which contained but a few Gaucher cells were in reality but sections of large ones depending on the plane of cutting. Moreover, while the wall of a sinus might appear complete in one section, examined in series, it was found to have numerous apertures in which the endothelium and stroma were deficient and by which communications between sinuses themselves and sinuses and pulp were established.

Moreover, serial sections revealed the fact that, although many of the Gaucher cells appeared free in the sinuses, actually few if any were really unattached. In large dilated sinuses filled with blood and lined by a single layer of Gaucher cells which rested directly on the basement membrane and were often separated by endothelial cells, one could demonstrate that any apparently free cells were portions of finger-like projections extending into the lumen from the cells which lined the wall. These projections were often quite long, made up of several, often multinucleated cells, and swung as long tongues within the sinus.

In order to bring out in greater detail the acidophilic and basophilic staining qualities of the cells, tissue which had been fixed in Orth's solution was sectioned and stained by Pappenheim's method. By careful differentiation, the exact point at which these cell characteristics were most definitely shown was ascertained. These sections were cut especially thin and mounted in neutral balsam.

Stained by this method, the Gaucher cells were definitely oxyphilic. The nucleus was a pale blue, sometimes almost invisible in the mature cells; while the cytoplasm was a yellowish pink and contained a slightly deeper staining, also yellowish pink spongioplastic network. Interesting, however, is the fact that transitional stages up to this mature cell were seen. These were especially pronounced about blood vessels which were devoid of any lymphoid mantel. Here, one found in the adventitia groups of cells interpolated between its fibrous tissue. These lay in chains made up of two, three or even more cells and running longitudinally in the vessel wall. These cells were medium-sized,

3. Wahl, H. R., and Richardson, M. L.: A Study of the Lipin Content of a Case of Gaucher's Disease in an Infant, Arch. Int. Med. **17**:238 (Feb.) 1916.

polygonal, often with flattened edges. Their cytoplasm was scanty, narrow and basophilic; their nucleus was relatively large and slightly irregular in outline to fit the shape of the cell, with reticular arrangement of the blue staining chromatin, which was aggregated into one, often more, nucleolus. These cells appeared to rise from other more definitely spindle-shaped, starlike cells which corresponded to the adventitial cells of Marchand. Cells showing transitional stages between the two were frequent.

Moreover, if one examined several of the cell strands described above, it was obvious that as one drew away into the perithelial tissue, the cell groups became larger until double rows of closely approximated cells appeared, and finally even irregular clusters. The majority of the cells of these groups remained at the same stage of differentiation, but one or two as a rule took on new qualities. They became larger as regards both cytoplasm and nucleus.

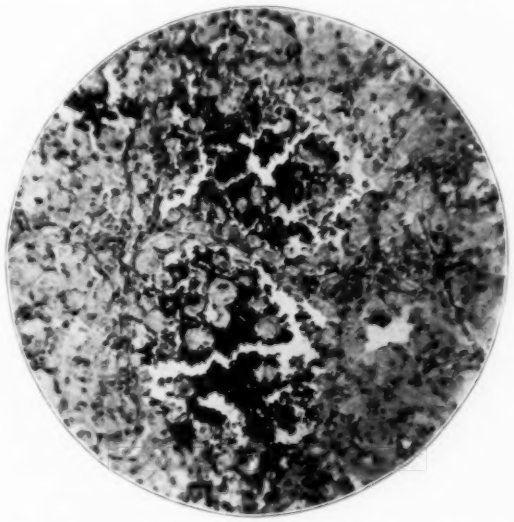

Fig. 4.—Photomicrograph showing large dilated sinuses lined by Gaucher cells. (Photo by Mr. Thomlinson)

The former was broad and nongranular, and stained predominantly blue, though there was a suggestion of pink mixed in; the latter was large, ovoid, vesicular, with a tendency for the chromatin to clump near the nuclear membrane. The cell at this stage strikingly resembled the embryonic myeloid cells (myeloblasts, leukoblasts) which are found in clusters in hyperplastic bone marrow.

In the irregular clusters of cells which lay between the strands and the more or less completely former alveoli of typical Gaucher cells, the transition between the myeloid-like cell described above and the Gaucher cell was completed. At the same time, others of the more embryonic cells in the strand took on myeloid differentiation. Thus irregular clusters of myeloid cells appeared here, which contained an occasional cell, larger and possessing a broader and more oxyphilic cytoplasm. It had lost its preponderance of blue and now was pink with but a tinge of blue. Moreover, the nucleus had become much larger, less clearly defined and often lobated to a degree, though not exactly polymorphous. It still showed clumps of peripherally arranged chromatin. From

this point, it was but a step to the typical Gaucher cell; the cell broadened, appeared flatter and lost its basophilic qualities completely, that of the nucleus being the last to go.

Although the process has been described in graded steps, this gradual transition from the smaller basophilic undifferentiated cell to the large oxyphilic, highly differentiated cell of Gaucher occurs in reality through fluid stages. Mitotic figures are scarce, but occasionally occur in the smaller, less differentiated cells of the strands. Interesting is the fact that here and there among the irregular clusters of myeloid-like cells, cells with eosinophilic granules were present. These, as in the bone marrow, were of two varieties, one having a rather large vesicular paler-staining nucleus which tended to polymorphism, and the other having a smaller more diffusely staining nucleus which remained in the myelocyte stage. Furthermore, occasionally though much more rarely, mononuclear cells with neutrophilic granules were observed. Both of these granular cells, together with mast cells, were preserved even in the large alveoli, where they lay apparently more or less crowded between the large, fully differentiated Gaucher cells.

The characteristic transition described above, however, was not limited to the perithelial areas of the larger and smaller arterioles. It was also evident in the endothelium lining the venous sinuses. Small sinuses could be seen in the less involved areas which were lined by large endothelial cells, protruding more or less into the lumen and showing the same alterations in size and varying degrees of oxyphilia described above. Furthermore, in the large alveoli filled with Gaucher cells very often the lining endothelium remained, showing the same progressive transition. Actual transition of the pulp cells to Gaucher cells could not be made out. Small irregular clusters of Gaucher cells could be seen which appeared in no apparent definite relation, to either the vessels or the sinus walls; but the same transitional stages were not observed in these clusters.

COMMENT

In a discussion of the histogenesis and nature of this interesting condition, it hardly seems necessary here to go into the detail as to the various views brought forward by different authors. They have been reviewed recently by Barat.[4] The original neoplastic conception has been quite generally discarded and recent study has concerned itself with the pros and cons of an endothelial or reticular origin of the characteristic cells. The facts associated with the argument are quite generally known as they have been gone over by numerous authors. The possible relation of the disease to the lipemias and cholesterin metabolism has been ably reviewed by Eppinger.[5]

There is one general outstanding feature of Gaucher's disease which appears to have been submerged somewhat in the detailed study of the cells themselves; and that is, that it is a disease of the hematopoietic system. Only those organs are involved which possess hematopoietic activity. They include primarily the bone marrow, spleen and lymph glands; and secondarily, other slumbering myelopotent areas in the liver, suprarenal, etc. They possess in common, and together constitute, the

4. Barat, Irene: Zur Histopathologie der grosszelligen Splenomegalie Typus Gaucher, Folia hematol. **26**, Arch. 3 (April) 1921.

5. Eppinger, H.: Die Hepato-lienalen Erkrankungen, Berlin, Julius Springer, 1920.

great bulk of the reticulo-endothelial tissue of the body. The intimate relation of this tissue, or better, reticulo-endothelial system, to blood formation is now well recognized. It would appear, therefore, at the start, from the location of the lesion, that it is related to some type of hematopoietic activity. Moreover, its racial, familial and congenital nature suggests a condition which either exists deep within the organic constitution of the individual, or is concerned with the earlier development in still embryonic processes. Last, not least, the obvious origin and development of the specific Gaucher cells from endothelial and perithelial parent cells, as shown by this early case, is in agreement with this conception. Sabin and others have demonstrated an early embryonic origin of the blood cells from these, and only these, sources. Moreover, in extra-uterine life, as Gruner puts it, it is the slumbering perivascular adventitial cells that acquire, by an upset of equilibrium, either lymphoblastic or myeloblastic tendencies.

If these considerations of the general nature of the disease, its location and the origin of the cells point to a hematopoietic lesion, let us further examine the evidence by the cytogenetic changes in the cells themselves. The nature of the transition from the adventitial cells of the arterioles and the endothelial lining cells of the sinuses is at first essentially that of myeloid metaplasia. The large cells with basophilic cytoplasm and large ovoid vesicular nuclei, correspond to the primordial myelopotent blood cell (the myeloblast of Naegeli, the lymphoidocyte of Pappenheim). From these, owing to deposition of paraplasm in the interspongioplastic network, there occurs a gradually increasing oxyphilia which leads the cytoplasm of the cell by stages to the point of granule formation. Coincidentally, the nucleus displays typical clumping of the chromatin away from the parachromatin, in contrast to the less differentiated cell, where a fine network exists. Moreover, many of the nuclei exhibit a tendency to lobation, which is characteristic of developing myeloblasts. Unfortunately, in sectioned tissue that has been fixed and hardened, these changes cannot be observed with the precision characteristic of observations on blood smears, but the coarse changes are obvious and are strikingly similar to the myeloid changes observed in any hyperplastic leukogenetic bone marrow. The absence of oxydase in these developing cells might appear a strong argument against their myeloid nature, but it is a fact that such cells do not give the oxydase reaction in tissue sections under various circumstances, until they have attained a higher degree of differentiation. This was very manifest in sections from a case of subleukemic sarcoid myelosis which we recently examined. Here, large areas of myeloid metaplasia were quite free from oxydase, while others gave very strong positive reactions. Its presence under pathologic conditions is, therefore, variable.

Approaching now the stage of granule formation within the cytoplasm of the cells, there occurs a notable deviation from normal myelopoiesis. The vast majority of the cells at this stage undergo a peculiar type of swelling associated with a diffuse oxyphilic transformation, involving first the cytoplasm and ultimately the whole cell. Thus, they acquire the typical Gaucher cell characteristics. No true granules are formed, though the whole cytoplasm assumes a granular-like composition. The presence of eosinophilic granular myelocytes closely associated with the other cells suggests the possibility that, as regards this particular line, the progress of cell development is regular. Furthermore, occasional neutrophilic and basophilic granular mononuclear cells are observed.

As to the exact physicochemical nature of the oxyphilic change, little can be said. Neither the idea of protoplasmic hypertrophy nor of albuminous deposition adds a great deal to our conception, and we should be inclined to look on it as an excessive continuation or perversion of the usual maturative activities that result in the discharge of acidophilic, broken-down products into the cell body.

Such a conception of perverse myelopoiesis, or dysmyeloplasia, is not without support from previously reported cases of the disease. If, with this conception in mind, we review the descriptions of various authors of their cases, we are struck by the number of otherwise unexplained facts that fit in with it. For example, in the case recently (1921) reported by Foot and Ladd,[6] attention is called to the acidophilic and hypertrophic condition of the adventitial cells of the smaller arteries. In the case described by Babes, Aurel and Babes (1913),[7] there is an extraordinary tendency to eosinophilia, there being not only many eosinophile polymorphonuclears present, but eosinophilic granulation of the large cells themselves. Mandlebaum,[1] in 1912, called attention to the eosinophil and neutrophil myelocytes in the involved lymph nodes. In the case reported by Mandlebaum and Downey,[2] in 1916, it is stated that the Gaucher cells are "particularly numerous just beyond the wall of the larger veins or within their adventitial coat," where these writers consider that they arise from connective tissue.

Moreover, the conception is not without support from other somewhat allied conditions. In myeloid metaplasia of the spleen, as Naegeli [8] and Pappenheim emphasize, the process takes origin from the perivascular connective tissue, more particularly from the slumbering clasmatocytes, which under specific irritation proliferate and differentiate to form

6. Foot, N. C., and Ladd, W. E.: Report of a Case of Gaucher's Splenomegaly, Am. J. Dis. Child. **21**:426 (May) 1921.

7. Babes, V.; Aurel, and Babes, A.: Un cas de maladie de Gaucher avec grandes cellules éosinophiles, Compt. rend. Soc. de Biol., No. 36, p. 575, 1913.

8. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1923.

at first embryonic and then more mature myeloid cells. The lymphoid areas are not involved primarily but are brought to atrophy eventually by the pressure on their periphery of the myeloblastic cells. In the liver, the initial seat of the transformation is the region of the liver capillaries. The general similarity of the two processes is striking. Noteworthy, also, though possibly with slight significance, is the fact that tuberculosis is by far the most commonly associated disease in both the myeloid leukemias and primary splenomegalies.

The very slight morphologic changes in, and the relatively normal appearance of, the circulating blood in Gaucher's disease might at first be considered as a strong argument against the hematopoietic conception. However, one must bear in mind that, as in the usual myeloid metaplasias, not the whole hematopoietic system is involved at once, but that the spleen, which is phylogenetically and ontogenetically the last of the blood-forming organs to give up its active blood-cell formation, is again the first to resume activity, and is followed later by the others. The bone marrow may continue for some time uninvolved. Furthermore, we are as yet quite ignorant of the factors which determine whether a pathologic cytoplasia shall remain aleukemic or become leukemic. These factors, it would appear, act more or less independently of the primary pathologic process. Thus, the sudden transition from aleukemic to leukemic conditions, as in lymphadenosis, is not attributable to any sudden change in the nature of the original lesions, but rather to some alteration of controlling influences. Thus, also, a normal blood picture is present in many diseases of the hematopoietic organs, as, for example, in multiple myeloma. Here, we deal with a systemic disease of the bone marrow itself, with normal and abnormal types of myeloid proliferation, and still the blood picture remains unaffected. Hence, may we not have quite as readily in Gaucher's disease, a normal and perverse myelopoiesis proceeding coincidently in separate organs without apparent alteration of the circulating blood?

Therefore, from the histologic studies of this early case, coupled with a review of previously reported cases and a consideration of allied conditions, we are inclined to the view that the splenomegaly of Gaucher is essentially a primary, probably congenital, progressive systemic disease of the hematopoietic tissues, characterized by an aleukemic dysmyelosis; that is, an irregular perverse myeloid metaplasia. The cells arise from the slumbering myelopotent cells of the reticulo-endothelial tissue of the hematopoietic organs. These are principally, and at first, the adventitial cells of the blood channels and the endothelium of the sinuses. Possibly, later, the closely related reticulum also takes on a similar activity. As to its etiology, little can be said. Its true cause, as that of other aleukemic and leukemic so-called blood diseases, awaits an explanation in a

clearer understanding of the finer details of embryonic and postnatal hematopoiesis, which is quite beyond the bounds of our present knowledge. However, its racial, familial, sexual and congenital characteristics, and its connection with the hematopoietic system, indicative of a deep-seated plasmic alteration, make the conception of Naegeli that it is a constitutional anomaly, that is, a mutation in the human species, worthy of consideration.

EXPERIMENTAL CHRONIC GLOMERULONEPHRITIS*

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In recent years, the problem of chronic nephritis has become, to some extent, restricted to the question of chronic glomerulonephritis. This type of kidney disease is almost undoubtedly of toxic or infectious origin, and, therefore, some measure of prophylactic treatment should be possible. With human material, obtained at necropsy, it is extremely difficult to trace the origin and development of this progressive nephritis, chiefly because, at different stages, the kidney presents various gross and microscopic appearances, seemingly distinct conditions; hence, the origin of the numerous classifications seen in clinical and pathologic descriptions. Were it possible to reproduce experimentally in one of the lower animals a condition in the kidneys simulating the chronic glomerulonephritis seen in man, a vast field of useful study would at once be opened, and great progress would be made in our knowledge of an extremely common and serious pathologic entity.

I. REVIEW OF THE LITERATURE

A review of the literature on chronic glomerulonephritis presents at once a difficult and disconcerting problem. It is impossible to avoid frequent reference to the extensive work on the production of experimental acute nephritis, because in many instances the same measures employed to cause acute changes have been tried with a view to effecting more lasting, or chronic, injury. Furthermore, throughout the earlier literature there is found but rarely any attempt to distinguish between chronic glomerulonephritis and chronic nephritis, the latter term being used to denote anything in the way of degenerative or inflammatory conditions which present the appearance of a chronic process. It is obvious, then, that even a careful review of the literature will still leave considerable confusion in the mind of the reader. No attempt has been made here to include everything that has been written or done on the problem of experimental chronic glomerulonephritis. What has been hoped for in the distillation and condensation of the mass of written matter is an arrival at a simple, clear and honest criticism in the light of present knowledge, for the benefit of future workers in this field.

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* This work was carried out in the John McCormick Institute for Infectious Diseases while the author was a Medical Fellow of the National Research Council in the Department of Pathology, University of Chicago, and Medical Resident at the Cook County Hospital, Chicago. The author is deeply grateful to Professor Ludwig Hektoen for extending all the privileges and facilities of the Institute.

The early studies on experimental acute nephritis brought out the interesting fact that some poisons injure the tubular epithelium severely, while others attack the glomerular capillary endothelium. Among the former poisons are uranium nitrate, potassium chromate and corrosive sublimate; while arsenic, cantharidin and snake venom belong to the latter group. Diphtheria toxin affects both glomeruli and tubules to nearly an equal extent. In the Harvey Lecture of 1910, Pearce [1] reviewed the early work, and pointed out that the different types of nephritis produced by means of these poisons were probably due to injury at different points of elimination. He insisted, however, that the distinction between so-called "tubular" and "vascular" poisons was not an absolute one, for already in 1907 Schlayer and his co-workers had shown, by physiologic methods, that the action of these poisons was more diffuse and less select than had been supposed. For example, in the late stages of uranium nephritis, a distinct disturbance in the vascular response was noted. Yet uranium was considered a good "tubular" poison. No one at present disputes the fact that one cannot injure the glomeruli seriously without simultaneously or subsequently damaging the tubules, and vice versa.

After these early experiences with acute nephritis, the above-mentioned poisons were used in the attempts to obtain a chronic nephritis. In 1904, Pearce tells us, Lyon tried cantharidin, corrosive sublimate and diphtheria toxin, known glomerular poisons. He found that the acute lesions disappeared rapidly and often recovery ensued. As Pearce states, if one includes in the term "chronic nephritis" a persistent kidney lesion characterized during life by elimination of albumin and casts, and histologically by changes involving glomeruli, tubules and connective tissue, nearly all experimental efforts can be excluded. It will be seen later how true this statement is.

Ophuls,[2] in 1907, reported on the effects of administration of lead salts by mouth in increasing doses over long periods of time. Guinea-pigs and dogs were used. Because of the anemia produced by the lead, it was difficult to keep the animals alive long. The guinea-pigs showed relatively unimportant renal changes. In dogs, marked chronic interstitial nephritis was found, yet there was no albuminuria nor cylindruria. Arteriosclerosis was not seen, and a true glomerulonephritis was not present.

Perhaps the poison most commonly employed in connection with experimental chronic nephritis was uranium nitrate. In 1909, Dickson [3]

1. Pearce, R. M.: Problems of Experimental Nephritis, Arch. Int. Med. **5**: 133 (Feb.) 1910.

2. Ophuls, W.: Experimental Chronic Nephritis, J. A. M. A. **48**:483 (Feb. 9) 1907.

3. Dickson, E. C.: Experimental Production of Chronic Nephritis in Animals by the Use of Uranium Nitrate, Arch. Int. Med. **3**:375 (June) 1909.

reported an extensive research with this substance. In eight guinea-pigs given from forty-six to eighty-seven doses of 0.25 mg. uranium nitrate, subcutaneously, over a period of from seventy-seven to 120 days, he found dilated glomerular tufts, with "cysts," some thickening of the capsule of Bowman and hyaline degeneration of the basement membrane. Round cell infiltration was noted but no fibrosis. In another series, of seven animals, which received 2.5 mg. doses of the poison at intervals of from ten to thirty days for periods of from seventy to 111 days, definite attacks of acute nephritis occurred, followed by recovery of the animals. In these, the surface of the kidney was found dimpled, new connective tissue had formed, and there was new elastic tissue around Bowman's capsule. A third series of fourteen animals received a single injection of 5 mg. of uranium nitrate, which resulted in a severe nephritis. While chronic changes were produced in some animals, there was a marked tendency to recuperation. Dickson stated that these lesions (described above) closely resembled subacute and chronic diffuse nephritis in man. It would be going too far, however, to say that he was dealing with a true glomerulonephritis. The same criticism applies to his work in 1912.[4]

As regards the actual morphologic effect of uranium on the glomeruli, we are indebted for our knowledge to Christian and his co-workers. In 1908, he pointed out the occurrence of peculiar hyaline droplets in the glomerular capillary endothelium of the rabbit kidney injured by uranium. This he considered a degenerative process. This peculiar lesion was limited to the specialized glomerular capillary. No other vessels in the body showed it. Later on, in 1913, Christian and O'Hare [5] summarized their extensive work on the actual anatomic changes in acute uranium nephritis in rabbits by stating that several types of glomerular lesions occur—hyaline droplets in the endothelium of the tuft, fibrin thrombi in the capillaries, hemorrhages into the tuft with slow coagulation, dilatation of Bowman's space with a granular material and proliferation of the endothelium of the tuft and, less often, of the capsular epithelium. The findings have been confirmed repeatedly.

In 1911, Christian [6] and his associates attacked the problem of producing chronic lesions in the glomeruli. Rabbits and guinea-pigs were given repeated doses of uranium nitrate or potassium bichromate for months. Round-cell infiltration was found quite constantly, while connective tissue increase occurred in the form of triangular foci running

4. Dickson, E. C.: Further Report on Production of Experimental Chronic Nephritis in Animals by the Administration of Uranium Nitrate, Arch. Int. Med. **9**:557 (May) 1912.

5. Christian, H. A., and O'Hare, J. P.: J. M. Research **28**:227, 1913.

6. Christian, H. A.; Smith, R. M., and Walker, I. C.: Experimental Cardiorenal Disease, Arch. Int. Med. **8**:468 (Oct.) 1911.

into the cortex from the periphery, the apex pointing inward. In these areas, the tubules were destroyed. The glomeruli were relatively little involved. This is an excellent description for the focal scars of "spontaneous" nephritis.

Further work with uranium was done by Baehr,[7] who, in 1913, published the results of the injection of a single, minute dose of uranium nitrate—from 0.35 to 0.8 mg.—subcutaneously in rabbits. His idea was to use just enough uranium to injure the glomeruli but insufficient to cause the usually extensive tubular degeneration. Of ten animals so treated, only one rabbit showed a definite glomerular lesion characterized by adhesion of the tuft to the capsule, epithelial crescents and albuminous exudate in Bowman's space. Apparently, this one animal was unusually sensitive to uranium. In eleven rabbits in which injection of from 0.35 to 0.8 mg. of uranium nitrate was made directly into one renal artery, extensive glomerular lesions were produced, affecting, in some cases, 40 or 50 per cent. of the glomeruli. Baehr described four stages in the affected glomeruli: coagulation necrosis of the capillaries, growth of the capsular epithelium to form a syncytium, secondary canalization of the glomerular mass by new capillaries and hyaline changes in the tuft with adhesions to the capsule.

In 1914, Wiesel and Hess,[8] working on a similar principle of small dosage of poison, injected seventy rabbits with uranium nitrate intraperitoneally and epinephrin intravenously. They produced swelling, hemorrhage and exudation in the glomeruli, with, later, proliferation, organization and contraction. Eventually, they state, contracted kidneys resulted. No one has ever been able to reproduce these findings. Roth and Bloss [9] repeated this work on sixteen rabbits, in 1922, but obtained only the usual tubular changes without significant glomerular changes except for hyaline droplets in the capillary endothelium in four animals.

Another substance which has been used to injure the glomeruli is snake venom. In 1909, Pearce [10] injected twenty-one rabbits with from 1 to 2 mg. of crotalus venom, in divided doses. All but one of the animals were killed within six days. The characteristic lesions were of two main types: hemorrhages into the tufts, but not into Bowman's space, and exudation of red cells, serum and fibrin, with or without hemorrhage. Hemorrhage into the tuft gave cystlike structures. Leukocytes were seldom seen. The tubular epithelium and the cells lining Bowman's capsule were not injured. The action of the venom

7. Baehr: Ziegler's Beitr. z. Path. Anat. u. z. allg. Path. **55**:545, 1913.
8. Wiesel and Hess: Virchows Arch. f. path. Anat., 1914.
9. Roth and Bloss: Virchows Arch. f. path. Anat. **238**:325, 1922.
10. Pearce, R. M.: J. Exper. Med. **11**:532, 1909.

was, therefore, selective on capillary endothelium, dissolving it, as had been previously shown by Flexner and Noguchi, in 1902.

Following up this work in 1913, Pearce[11] injected twenty-four rabbits repeatedly with the crotalus venom. No animal could be kept alive more than six or seven weeks. In the kidneys of these animals, there was noted proliferation of the endothelium of the tufts. The above mentioned hemorrhagic and exudative lesions were also present. Proliferation was not seen in the exudative type but was present in the hemorrhagic form. In other words, there was simply an organization of the thrombus. In those animals which lived the longest (from twenty-six to thirty-eight days), little glomerular change was found, although tubular degeneration was extensive. In dogs, the venom was much more fatal than in rabbits. Only tubular degeneration was produced, with hyaline changes in the glomerular capillaries. No evidence of reparative or subacute glomerular lesions was seen in dogs. Pearce concluded that the early lesions produced by crotalus venom did not tend to become chronic.

More successful results have been reported in 1921 by Suzuki.[12] He used "Habu" venom (Trimeresurus flavoridis, Hall). This is said to produce marked glomerular injury, with little tubular damage. Rabbits were given from 3 to 4 mg. per kilogram of body weight, intravenously. The susceptibility of the animals varied considerably as to the lethal dose and the effect on the kidneys. In animals dying within a few days, "cysts" appeared in the glomeruli, due, the author claims, not to rupture of the tuft but to extreme dilatation of one of the capillary loops. These "cysts" usually contained red cells, fibrin and a mass of what was probably platelets—apparently a thrombus. There was usually only one "cyst," occupying from one-third to one-half of the glomerulus ordinarily. Only one-quarter of the glomeruli were involved. In animals that lived more than a week, marked endothelial proliferation was noted. After from ten to fourteen days, degenerative changes appeared in the arterioles of the kidney, while the tubules underwent atrophy. After five or six weeks, an increase in the interstitial tissue was noted, particularly about Bowman's capsule. Fine granulation (or pitting?) of the surface of the kidney was seen. According to Suzuki, these "Schrumpfniere" are produced by the obstruction to the flow of blood through the glomerulus in the early stages, while the tubular atrophy and fibrosis are secondary phenomena. The capsular epithelium changes little. Epithelial crescents are not described by Suzuki. This nephritis does not tend to become progressive. Con-

11. Pearce, R. M.: J. Exper. Med. **18**:149, 1913.

12. Suzuki, T.: Mitt. a. d. Path. Inst. d. kais. Univ. z. Sendai, Japan **1**:225, 243, 1919-1921.

siderable recovery occurs within a few months. To speak of these kidneys as "Schrumpfniere," when they are not at all contracted, is somewhat far-fetched.

Suzuki was, apparently, not satisfied with the chronic changes noted above and went on to attempt to produce a chronic glomerulonephritis. He injected (A) eight rabbits with one or more large doses of "Habu" venom, and (B) more than twenty rabbits with one or more moderate doses. In the B group, the left kidney was removed surgically some time after the first injection and studied as a control for the earlier changes in the kidneys. The animals were allowed to live many months. According to Suzuki, granular kidneys were produced; yet the gross description of these kidneys corresponds well with that which will be given later for the so-called "spontaneous" nephritis of rabbits. Tubular changes are described in great histologic detail. In fact, the author goes so far as to divide the kidney lesions into "chronic parenchymatous" and "chronic interstitial" types, the former type being the one with little glomerular change. When one kidney was removed, the other showed much more atrophy and "contraction," which Suzuki blames on the effects of retained metabolic waste-products since the "Habu" poison could not act so long. Yet the atrophic areas were always focal, not diffuse, and not progressive lesions. In spite of the lengthy descriptions, discussions and speculations of Suzuki, one does not get the impression that he has produced a glomerulonephritis of the chronic variety. Unfortunately, there are no illustrations in his articles.

Diphtheria toxin has been frequently used in connection with experimental nephritis. Bailey,[13] in 1917, injected rabbits with diphtheria toxin alone, or in combination with pituitary extract. In some animals, a high grade of degenerative arteriosclerosis was found, affecting, chiefly, the media in all the large vessels. In the kidneys were found swelling and desquamation of the endothelial cells, fibrin thrombi and hyaline masses in necrotic capillaries of the tufts, with hemorrhages in some; and, in some glomeruli, collections of polymorphonuclear leukocytes. Bailey believed that these changes resembled closely those found in acute and subacute glomerulonephritis in man. But this interpretation is questionable. There were no proliferative changes.

In the same year, 1917, Faber[14] carried out an extensive study on twenty-three rabbits, all of whom died or were killed within ten days. He injected from 0.001 to 0.02 c.c. of diphtheria toxin (1 c.c. containing 200 minimum lethal doses). According to him, the primary change, with a small dose, was endothelial proliferation in the tuft. With larger doses, degenerative changes set in, until finally the glomerular capil-

13. Bailey, C. H.: J. Exper. Med. **25**:109 (Jan.) 1917.
14. Faber, H. K.: J. Exper. Med. **26**:139 (Aug.) 1917.

laries ruptured and globular hemorrhages into the tuft, the so-called "blood-cysts," occurred. The characteristic lesion of human hemorrhagic glomerulonephritis—fibrin, red blood cells and leukocytes in the capsular space—was notably absent. At most, the only exudate was albuminous. With still larger doses, thrombotic masses formed, probably necrotic cytoplasm of the endothelium. Leukocytes were scarce. Tubular changes were apparently secondary to the glomerular injury and did not dominate the picture.

As regards the production of chronic changes with diphtheria toxin, there is the difficulty of keeping animals alive for more than a few weeks. Frothingham,[15] in 1914, injected animals repeatedly with sublethal doses of diphtheria toxin. He reported failure to produce any significant changes in the kidney with such injections.

With an increasing knowledge of the etiologic factors involved in human glomerulonephritis, especially the acute form, it was but natural that bacteria or their toxins be employed in experimental production of nephritis. All will admit that scarlet fever, bacterial endocarditis and severe sore throats are often followed by glomerulonephritis. The organism involved is probably of the streptococcus group—sometimes the hemolytic type, sometimes the anhemolytic or viridans variety. Experimenters have employed various organisms in the attempt to produce kidney lesions. Some have reported successful results; others have been guarded in their opinions, and a few have confessed failure or, at least, skepticism in their interpretation of the facts.

Le Count and Jackson,[16] in 1914, studied the effect of streptococci on the rabbit's kidney. Fifty-eight animals were given a single injection of living organisms—hemolytic streptococci, from cases of streptococcus sore throat in fifty-one rabbits. In ten animals, no changes were found. In sixteen, acute changes were seen: bacterial emboli in the capillaries, areas of necrosis in the pyramids; acute disorganization of the glomeruli with fibrin thrombi and hemorrhage in some glomerular spaces in only one animal. Apparently, the lesions in the glomeruli healed. Subacute changes were noted in thirty-two rabbits, in the form of lymphocytic and plasma cell exudates about the veins. In twenty-two animals, there were chronic changes—focal scars with dilated tubules, retention cysts and focal regenerative changes. These chronic changes would be rather difficult to distinguish from the "spontaneous" nephritis described by Le Count and Jackson in their article.

Klotz[17] in 1914, injected thirty-four rabbits from one to five times over a period of from two to 228 days with *Streptococcus viridans*

15. Frothingham: J. M. Research **30**:365, 1914.
16. Le Count, E. R., and Jackson, L.: J. Infect. Dis. **15**:389, 1914.
17. Klotz: Tr. Ass'n. Am. Phy. **29**:49, 1914.

isolated from cases of endocarditis. He described acute and chronic changes in the kidneys, acute and chronic interstitial nephritis, the latter resulting from the former and quite indistinguishable from our present conception of "spontaneous" nephritis. Klotz attempted to draw an analogy with the nephritis in man. It is perfectly obvious that he was not dealing with a chronic glomerulonephritis.

Using *B. mucosus-capsulatus*, Major,[18] in 1917, injected twenty-one rabbits. Twenty animals showed lesions. A single injection in five rabbits produced acute hemorrhagic nephritis (?)—red blood cells in the glomerular spaces, tufts, tubules and interstitium. Hyaline fibrin thrombi were seen early in the glomerular capillaries. In animals which received repeated injections, marked tubular changes were found, with lymphocytic collections. Occasional fibrotic glomeruli were observed. In another group, the kidney was granular (pitted?) under the capsule, with numerous areas of round-cell infiltration, dilatation of the tubules and desquamation of the epithelium, fibrosis and destruction of glomeruli. Fibrosis around the glomeruli and the early stages of crescent formation were also seen.

Winternitz and Quinby,[19] in 1917, injected *B. bronchisepticus* directly into the renal artery of dogs. They obtained chiefly interstitial changes. Involvement of the glomeruli was not general enough to produce marked changes.

In 1920, Kuczynski [20] inoculated mice repeatedly with streptococci. He described glomerular changes, degeneration of the tufts, followed by proliferation and hyalinization. All this was considered a defensive process. The intermediate stages were not described by the author. Hyalinized glomeruli are not uncommon in ordinary mice.

In contrast to some of the foregoing results, there was the report of Faber and Murray,[21] who, in 1917, injected a series of thirty-seven rabbits with various organisms—*Streptococcus hemolyticus* (twenty rabbits), *Streptococcus viridans*, *B. coli* and the staphylococcus. They failed to produce glomerulonephritis.

Pappenheimer and others [22] injected hemolytic streptococci directly into the renal artery of the rabbit. Only acute changes were produced. The micro-organisms disappeared rapidly, through the action of the phagocytes. Within a few hours many leukocytes were seen in the glomeruli, and later on suppurative foci appeared; but chronic changes were not obtained.

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18. Major, R. H.: J. M. Research **37**:125 (Sept.) 1917.
19. Winternitz, M. C., and Quinby, W. C.: J. Urol. **1**:139 (April) 1917.
20. Kuczynski: Virchows Arch. f. path. Anat. **227**:186, 1920.
21. Faber, H. K., and Murray, V.: J. Exper. Med. **26**:707 (Nov.) 1917.
22. Pappenheimer et al.: Proc. New York Path. Soc. **16**:73, 1916.

In connection with the foregoing work, the experiment of Bloomfield,[23] in 1919, must be mentioned. He injected dead organisms (*Streptococcus hemolyticus* and *viridans*) directly into the left renal artery of rabbits. At this operation, the kidney was examined closely for the presence of "spontaneous" nephritis. About two weeks later, a series of intravenous injections of living organisms was begun, from one to nineteen injections over a period up to fifteen months. The results were entirely negative as regards chronic changes in the kidneys. Of course, Bloomfield was not misled by the "spontaneous" nephritis present in his animals. In twelve of sixteen animals, the kidneys looked exactly the same after as before the injections of bacteria.

Using only bacterial poisons, to rule out the factor of embolism and to make possible more diffuse injury of the kidneys, Stoddard and Woods,[24] in 1916, injected toxins obtained from cultures of streptococci and staphylococci; also Vaughan's split-protein poisons. Rabbits were given such injections repeatedly. No glomerular changes of note were produced.

Combinations of a metallic poison, or diphtheria toxin, with bacteria have also been employed in experimental nephritis, with the idea of establishing a site of lowered resistance in the glomerulus, where bacteria or their toxins could then gain a stronger foothold. Following the example of Opie, who, in 1909, found it much easier to produce cirrhosis of the liver in animals by the combined use of chloroform and *B. coli* than by either one alone, O'Hare,[25] in 1913, repeatedly injected both uranium and *B. coli* into rabbits. Eighteen of forty animals lived from a few weeks to five months. A varying amount of scarring was produced in the boundary zone and in the cortical rays of the kidney. Lymphocytic infiltration was not marked. The glomeruli were drawn together in the scars and showed variable changes: dilatation of the capsular space; shrinking and thickening of the capsular wall, and, occasionally, proliferation of endothelium. Arteriosclerotic lesions were not found. The fibrosis thus produced was more constant than that found in animals which received only uranium nitrate. Yet all the foregoing results can be duplicated in animals by "spontaneous" nephritis, and, regardless of the origin of the scars, one is not dealing here with a glomerulonephritis. From the latter standpoint, O'Hare's results were negative.

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23. Bloomfield, A. L.: Bull. Johns Hopkins Hosp. **30**:121 (May) 1919.

24. Stoddard, J. L., and Woods, A. C.: J. M. Research **34**:343 (July) 1916.

25. O'Hare, J. P.: Study XVII: Experimental Chronic Nephritis Produced by the Combination of Chemical (Uranium Nitrate) and Bacteria (B. Coli Communis), Arch. Int. Med. **12**:49 (July) 1913.

In 1917, Major [26] injected young rabbits repeatedly with killed cultures of *Staphylococcus aureus*, over a period of a few months. In each case, a preliminary dose of 0.5 mg. of uranium nitrate had been injected. Six of seven rabbits developed well-marked lesions in the kidneys: round-cell infiltration, diffuse fibrosis and varying destruction and fibrosis of glomeruli. No such changes were seen in six rabbits given only the uranium nitrate. The author concluded that chronic nephritis could be produced thus. Grossly, the kidneys showed puckering and scarring. The interpretation of the findings here is somewhat open to question.

In the same year, Faber [27] injected ten rabbits with varying small doses of diphtheria toxin, followed in from one to three days by *B. coli*, intravenously. A true fibrinous exudate was found in Bowman's space, some red cells and desquamated epithelium. Frequently, masses of fibrin were seen in the glomeruli. Leukocytes were found in large numbers in the tuft, and occasionally in the capsular space. Early, half-moons appeared. With *B. coli* alone, no notable changes could be produced. Apparently, exudation was more marked when both toxin and organism were used than when the latter alone was employed. With Vaughan's split-protein instead of *B. coli*, similar results were obtained, but there was no leukocytic reaction. While Faber was apparently much more successful than most other experimenters in obtaining a severe exudative type of glomerular lesion, he did not allow his animals to develop chronic changes. They were kept alive for only a few days.

A new phase of experimental chronic nephritis was exposed by Newburgh,[28] in 1919. He fed rabbits a high protein diet, egg-white, casein and soy bean representing the protein constituents. Renal injury, shown by albuminuria and cylindruria, was quickly produced. Histologically, the changes were those of acute, subacute and chronic tubular changes, with secondary increase in interstitial tissue. The glomeruli and renal blood-vessels showed little change. The experimental conditions were rather artificial.

In view of the clinical association of acute nephritis with exposure to cold, Gaisböck,[29] in 1922, experimented on the effects of direct cooling of the kidneys in animals. Tubular and glomerular degeneration occurred early, but eventually healing took place, and progressive or chronic changes were not obtained in this manner.

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26. Major, R. H.: J. M. Research **35**:349 (Jan.) 1917.
27. Faber, H. K.: J. Exper. Med. **26**:153 (Aug.) 1917.
28. Newburgh, L. H.: Production of Bright's Disease by Feeding High Protein Diet, Arch. Int. Med. **24**:359 (Oct.) 1919.
29. Gaisböck, F.: Wien. Arch. f. inn. Med. **3**:1 (Nov.) 1922.

An admirably critical review of the entire field of experimental nephritis was published by Roth and Bloss,[9] in 1922. They begin with what seems to be the most logical introduction to experimental chronic nephritis, namely, "spontaneous" nephritis, as it exists in various animal species. Veterinary authorities agree on two points: the frequency of acute nephritis or nephrosis, and the rarity of glomerulonephritis. Henschen,[30] in 1921, reported the condition of the kidneys of 200 dogs and more than fifty cats on which he performed the necropsy. He stated that degenerative conditions, or nephroses, were quite common, except amyloid degeneration. The most usual form of acute nephritis he called acute interstitial lymphatic nephritis. Here, there are lymphocytic infiltrations, which later become fibroblastic. Glomeruli atrophy and become hyalinized, their capsules thicken and the tubules atrophy, all forming a scar which corresponds, grossly, to a depression, or pit, on the surface of the kidney. Renal atrophy, of a focal character, was commonly found in dogs, but produced no symptoms. Arteriosclerotic changes could not be demonstrated. Acute nephritis occurred frequently in puppies.

Roth and Bloss discuss the rarity of true chronic nephritis in animals generally. Thus, in 7,000 necropsies on sheep, only twenty-three cases of chronic nephritis were found. A true diffuse glomerulonephritis practically never occurred. The authors, further, draw a distinction between the various degenerative changes described in experimental nephritis and the inflammatory exudative process seen in the true glomerulonephritis in man. They comment on the rarity of exanthems and rheumatic diseases in animals. This factor—the difference in etiology—might explain the differences in the pathologic pictures in man and animals. In ten cases of hog cholera, in some of which a severe endocarditis had occurred, no true glomerulonephritis was found. Nor could such a nephritis be produced in rabbits by means of the hog cholera organism. In conclusion, they refer to inherent differences between experimental animals and man as a probable cause of the failure to produce glomerulonephritis.

Many of the authors referred to throughout this review of the literature have discussed the so-called spontaneous nephritis as it occurs in rabbits, the animals most commonly used. Excellent descriptions have been given by Le Count and Jackson,[16] Bloomfield [23] and Bell and Hartzell,[31] not to mention the reports in the earlier literature on experimental nephritis. The characteristic lesions vary, according to the stage at which they are observed. In the early stage, one finds microscopically, a varying amount of round cell infiltration about the smaller

30. Henschen, F.: Acta med. Scandinav. **53**:774 (Jan.) 1921.
31. Bell, E. T., and Hartzell, J. Infect. Dis. **24**:628 (June) 1919.

veins, usually in the boundary zone or extending along the vessels upward into the cortex. In the areas of infiltration, the tubular epithelium undergoes necrosis, with resulting atrophy or dilatation of the portion of the uriniferous tubule above the areas. Grossly, one may see no change in the kidneys, but where the infiltration has extended up into the cortex, a plum-colored pin-point or pinhead-sized spot can be seen through the capsule. Eventually, fibrosis sets in, causing distortion of the atrophic or dilated tubules in that area, a drawing together of the glomeruli, and the formation of a narrow or broad wedge-shaped scar which extends from the surface of the kidney down through the entire cortex, causing a depression or pit of varying diameter on the surface of the kidney. The glomeruli are usually shrunken in these scars, but never show anything corresponding to glomerulonephritis. There is occasionally a fibrotic glomerulus. Usually there is, at best, some fibrosis about Bowman's capsule. Within these scars are varying numbers of round cells and degenerating tubular epithelium. These scars are always focal, with entirely normal intervening kidney tissue, and even in extreme cases represent only a minority of kidney tissue. Both kidneys are usually involved to the same extent. In extreme cases, the kidneys may be so pitted and puckered as to give a superficial resemblance to granular kidneys. The capsule is never firmly adherent over these pits. Associated with this cortical scarring may be similar focal scars extending all the way down the medulla.

As regards the frequency with which this condition is found, variable percentages are given in the literature, ranging from about 10 to about 90 per cent. The frequency of "spontaneous" nephritis is, according to Bloomfield,[23] quite independent of the age, size, weight or sex of the rabbit. It is more dependent on the particular lot of animals one is dealing with. But even from 40 to 50 per cent. would be a fair average of incidence for most laboratory rabbits.

The etiology is not known. The lesions are apparently embolic in character. Yet, even in relatively late stages, some patent vessel may be seen in the involved area. The rabbit is subject to a sufficient number of infections to make focal embolic lesions possible.

The "spontaneous" nephritis of rabbits has absolutely no resemblance to the human progressive, or chronic, glomerulonephritis. None but a novice in pathologic histology should have any difficulty in distinguishing between the two. Yet a detailed and lengthy description has been given, because, time and again, experimenters have, in all faith, reported, and illustrated with photomicrographs or drawings, what to them was an artificially produced chronic nephritis (comparable to the human type), but what, in the light of present knowledge, could only have been the "spontaneous" variety. Whether or not injections of

bacteria, toxins, or metallic poisons, or what not, can produce scars similar to those occurring "spontaneously" cannot be determined. But it makes no difference either way, because, even if they were so produced, they would represent only a focal chronic nephritis from which the animal would never be in danger of acquiring uremia, cerebral apoplexy or cardiac failure—the Three Fates of human beings with chronic progressive glomerulonephritis.

II. OBJECT OF THIS RESEARCH

Realizing fully the numerous failures in the field of experimental chronic glomerulonephritis, but encouraged somewhat by the definite knowledge regarding the injury of glomeruli by certain poisons, and stimulated by the vast importance of the ability to reproduce, experimentally, in a constant fashion and under controlled conditions, a pathologic process simulating the progressive glomerular disease in man, it was thought worthwhile to undertake the problem, along lines suggested by Prof. H. G. Wells. The object, therefore, of this research was the production of a chronic glomerulonephritis in an experimental animal. The success of the experiment was to be gaged chiefly by the actual, visible gross and microscopic pathologic changes in the kidneys.

III. METHODS OF PROCEDURE

Several methods were tried:

1. The injection, intravenously, of relatively large doses of an organism of low virulence—*Streptococcus viridans* isolated from a "granule" in an infected tonsil which had been removed surgically. This organism was kept growing on blood-agar slants from which it was transferred to tubes of dextrose ascitic broth and grown for twenty-four or forty-eight hours before being used. The contents, from 6 to 10 c.c., of these tubes were centrifuged at high speed for a few minutes, the culture liquid poured off and the organisms suspended in from 2 to 3 c.c. of physiologic sodium chlorid solution, this dose being then injected, every two or three days, into the ear veins of rabbits, as long as they lived. Occasionally, subcutaneous injections were interpolated or substituted.

2. The use of diphtheria toxin, in varying dosage and frequency, in an attempt to cause considerable circulatory disturbance in the kidneys and, thereby, favor the localization and activity in the glomeruli of bacteria present in the blood-stream. The bacteria used were the strain described in the preceding paragraph, and the injections were given in a manner and dosage similar to those there described.

3. The use of rattlesnake venom in a manner similar to the diphtheria toxin, and for the same purpose, in view of the glomerular injury

described in the literature, along with the periodic injection of the same strain of *Streptococcus viridans*, and in the same manner as employed in the first method described.

4. The injection, every two or three days, of organisms directly into the heart (left ventricle or auricle as far as possible), in order to give a higher concentration of bacteria in the blood-stream and to obviate the pulmonary filter. The organisms used here were also of the *Streptococcus viridans* type, but a different strain, having been isolated from the blood of a patient with subacute bacterial endocarditis, but grown in the same manner and injected in about the same amount as in the previously described methods.

5. The injection of a suspension of organisms (the same strain of *Streptococcus viridans* as described in the fourth method) along with lycopodium spores, directly into the left renal artery, under anesthesia, surgical asepsis and free exposure of the left kidney. The object here was to plug up the very small vessels with the spores, and perhaps, in that manner, force the bacteria to remain longer, and in large numbers, in the kidney, giving them an opportunity to do their worst, so to speak. The spores, in themselves, are quite inert.

Rabbits were the only animals used. The urine was examined usually for two consecutive days previous to beginning the experiment, occasionally during a series of injections to note any possible changes, and always at necropsy if urine was present in the bladder. The animals were never catheterized. They were kept two in a cage, except when urine was to be obtained. Hygienic conditions were such that no epidemics of any sort developed among these animals during the course of a year. All of the animals, except those in which injection was made directly into the renal artery, were allowed to die, that is, were not killed. All were subjected to postmortem examination as soon as possible after death; usually in less than 24 hours. The tissues were fixed in Zenker's fluid, imbedded in celloidin and stained with hematoxylin and eosin.

IV. RESULTS

1. Twenty rabbits were given intravenous injections every two or three days of a suspension of *Streptococcus viridans*, isolated from a removed tonsil. Of this series, all the animals lost from one-sixth to one-third or more of their body weight, but otherwise showed no definite symptoms. Following the injections, there were occasionally albumin and casts in the urine. At necropsy similar inconstant findings prevailed. Ten rabbits lived less than twenty-five days; five rabbits lived between twenty-five and seventy-five days; while five lived between seventy-five and 145 days. The highest number of injections was forty-five.

In none of the kidneys of this series was there any suggestion of an acute, subacute or chronic glomerulonephritis. Outside of some granular precipitate in the capsular spaces of some glomeruli, nothing abnormal was found in the glomeruli. Solitary small infarcts were found in the kidneys of three animals, which lived, respectively, fourteen, sixty-nine and seventy-six days. In the first and last of these three, there was also a vegetative mitral endocarditis. In another rabbit, which lived twenty-five days after the first injection, and had an extensive vegetative aortic endocarditis, a microscopic abscess involving a glomerulus was found in one kidney. In fifteen of the twenty rabbits were found one or more of the various stigmas of "spontaneous" nephritis: perivascular and interstitial round cell infiltration, fibrosis in the boundary zone and medulla, focal longitudinal cortical scars, etc. Definite focal scars were found in eleven of the animals. Gross pitting of the surface of the kidney was seen in seven rabbits: in one of the ten that lived less than twenty-five days; in two of the five that lived between twenty-five and seventy-five days, and in four of the five which lived between seventy-five and 145 days. One is tempted to draw conclusions from the foregoing figures, in regard to the connection between focal scarring or spontaneous nephritis and the repeated injection of bacteria. Of the three rabbits in which the kidneys were entirely negative from every point of view, the one living longest died within eight days.

In seven of these rabbits, which lived eight, fourteen, twenty-five, fifty-nine, seventy-two, seventy-six and 145 days, respectively, a vegetative endocarditis was present, which was never ulcerative. The vegetations were large, white and firm, on the mitral valve in all but one (aortic) rabbit. In the animal which lived 145 days, fibrous organizations had already occurred. Marked stenosis was found in some of the mitral orifices.

2. Forty-nine animals were injected with both diphtheria toxin and *Streptococcus viridans*. Except in the case of five rabbits, the diphtheria toxin was given subcutaneously, instead of intravenously, because the effects on the kidneys were the same and the animals lived longer. The bacteria were injected intravenously, every two or three days. The toxin used contained 1 minimum lethal dose (for a guinea-pig) in 0.015 c.c. The susceptibility and reaction of the animals to the diphtheria toxin varied extremely.

Fourteen of fifteen rabbits which received one or two doses of from 0.75 to 4.0 of a minimum lethal dose (the latter in only two animals, one dose each) of the toxin, in addition to the intervening bacterial injections, died within eleven days. Of the remaining thirty-four animals in this series, which at from five to nine day intervals received

toxin in a dosage of from 0.3 to 0.5 of a minimum lethal dose subcutaneously, thirteen rabbits lived less than ten days; nine lived between ten and twenty days; six between twenty and thirty days; four between thirty and forty days; and two, forty-six and forty-seven days, respectively. Some of the animals lost up to two-fifths of their body weight. Most of them lost one-third.

The kidneys showed varying changes. In some animals, a small dose produced tremendous changes. In others, e. g., the rabbit that lived forty-six days and received a total of 2.6 of a minimum lethal dose of toxin, practically nothing was found. In general, there were seen extreme hyperemia and dilatation of the glomerular capillaries, endothelial degeneration, hyaline thrombosis in some of the loops, and, what was very conspicuous but present in only sixteen of the forty-nine animals, globular glomerular hemorrhages into the tuft itself, giving the so-called "blood cysts." There was a varying amount of granular precipitate in the capsular space. Only occasionally were red blood cells seen in Bowman's space. Tubular degeneration was marked and numerous casts were seen in the kidney sections and found in the urine. In spite of all these acute changes, there was no leukocytic reaction to speak of. There was absolutely no proliferative reaction on the part of Bowman's capsule. In some of the animals that lived longer than two weeks, there was evidence of endothelial regeneration in the tuft, but it was not striking.

In four rabbits, a striking picture was seen: a mass of fibrin encircling the glomerulus entirely, or only a part of it, fingering in between the loops of the tuft, at times forming part of an old blood cyst, sometimes entirely within the tuft proper, or else lying free in Bowman's space, with often a hyalinized exudate contiguous with it and extending into the first portion of the tubule as a hyaline cast. This evidently represented an older stage of development than the changes described above, but it was found in animals living seven, sixteen, twenty-seven and thirty-seven days, respectively. Yet no epithelial crescents were ever seen in these kidneys, nor a significant leukocytic reaction.

One animal lived forty-seven days, receiving a total of 4.9 minimum lethal doses of diphtheria toxin and thirteen injections of bacteria. The kidneys of this animal were finely pitted, grossly, and were very firm. Microscopically, there was seen a marked type of "spontaneous" focal scarring. But, in addition to this, there was considerable diffuse interstitial tissue increase, marked variation in the size of the glomeruli, pericapsular fibrosis and connective tissue invasion of glomeruli outside the focal scars and, at times, adhesions between some loop of a tuft and Bowman's capsule. Numerous hyaline casts were present in the tubules and in the urine. The glomerular change here was not general

enough to be satisfactory. There were no true epithelial crescents. Consequently, even here one is not dealing with a true chronic glomerulonephritis, but rather with a chronic interstitial process.

All of the changes described so far have been produced by diphtheria toxin. What about the effect of the bacteria localizing in these injured glomeruli, with their tremendous congestion and hemorrhage? The bacteria seemed to have no effect at all on these glomeruli. There is nothing one could ascribe to their action on the glomeruli. Mycotic emboli were found in many of the glomeruli and in the afferent arteries, in the vessels of the lungs and even in the myocardium, in one animal which had received four minimum lethal doses of toxin intravenously, and the next day, when in an almost moribund condition, was given bacteria intravenously, death ensuing in twenty-four hours. There was no reaction about these bacterial masses. Probably, the circulation was in a failing condition when the organisms were injected, and the animal's resistance was nil. In all the other animals, the bacteria had no more effect on the damaged glomeruli than they had on the normal glomeruli of the first series. This result was very surprising, but the objective data were quite convincing.

Twenty-seven of the forty-nine rabbits showed the earmarks of "spontaneous" nephritis, whether truly spontaneous or not. In seventeen animals, definite focal scars were present. In twelve, grossly visible fine or coarse pitting on the surface of the kidneys was noted, in two of twenty-eight animals that lived less than ten or eleven days; in three of nine rabbits that lived between ten and twenty days; in four of six rabbits that lived between twenty and thirty days; in two of four rabbits that lived between thirty and forty days, and in one of the two rabbits that lived forty-six and forty-seven days, respectively. The other rabbit of the two had microscopic focal scars. Here, again, there is a temptation to draw conclusions, but one must be careful, because pitting occurred in animals that lived only two days and seven days, respectively; while extreme scarring and deformity of the kidneys were seen in an animal that lived only eleven days; obviously too short a period for even an enthusiastic concluder.

Endocarditis of the vegetative type was found in only three rabbits of this series. They lived fifteen, eighteen and forty-seven days, respectively. In the first animal of the three, there was an extensive infarction of one kidney, with multiple glomerular abscesses in that area. In the rabbit which lived eighteen days, a marked aortic endocarditis was present.

Arteriosclerosis was not produced, in spite of the relatively large number of animals used, the large doses of diphtheria toxin given and the considerable period of time many of the animals lived.

3. A series of twenty-six animals received from one to eight injections of rattlesnake venom—a total of from 10 to 66 mg. of the poison—subcutaneously. The usual bacterial suspension was injected intravenously, every second or third day. In two animals, a small dose of the venom, given intravenously, caused death within from two to three minutes, after convulsions. The subcutaneous injections always produced an extensive necrosis, particularly of the muscles, even at a great distance from the site of introduction of venom. All the animals lost considerably in weight.

Of the twenty-six rabbits, six lived between one and five days; fourteen between five and ten days; five between ten and fifteen days, and one for forty days. Postmortem changes set in very rapidly in these animals. As regards the kidneys, beyond hyperemia and degeneration of glomerular endothelium, with a granular precipitate in Bowman's space in some instances, there were no significant glomerular changes. This was surprising in view of the hemorrhagic and exudative lesions described by some authors.

Nine of the twenty-six rabbits showed evidence of "spontaneous" nephritis, but only one animal had kidneys which were extremely scarred and pitted grossly. Yet this animal had lived only nine days after the beginning of the experiment; so that one could not very well blame the experimental procedure for the pathologic condition found.

Mitral endocarditis was present in three rabbits, which lived four, eight and thirteen days, respectively. There were only a few small vegetations in each instance.

4. Direct intracardiac injections of a strain of *Streptococcus viridans*, isolated from the blood of a patient with subacute bacterial endocarditis, were carried out on ten rabbits. Two of these lived less than ten days; six between ten and twenty days, and two, twenty-four days. The number of injections varied from three to nine. The cause of death in all the animals was a more or less gradual deposition of layers of clotted blood within the pericardial cavity, distending it tremendously. Within these clots were masses of bacteria in microscopic abscesses. Four rabbits developed a definite vegetative endocarditis, never ulcerative in spite of the trauma to the endocardium during the repeated injections. The endocarditis was present only in animals that lived more than ten days, and in 50 per cent. of these.

The kidneys showed no more changes than those in the animals of Series 1. No glomerular lesions of any sort were encountered. In one of the rabbits that developed endocarditis, a small infarct was found in one kidney. In this series of ten animals, only two showed spontaneous nephritis. In only one was gross pitting evident.

5. Direct injection of a bacterial suspension (the same organisms as in Series 4) with lycopodium spores into the left renal artery was carried out on twenty-six animals successfully. They were allowed to live from nineteen to sixty-five days, when they were killed by a blow on the back of the neck, and necropsy was performed immediately. Most of the animals maintained their body weight and some actually gained following the operation. No injections were given other than the one into the renal artery. Five rabbits lived less than ten days, and in all of these, the left kidney was more or less completely infarcted, owing partly to injury to the vessels at operation and partly to obstruction of branches of the renal artery by masses of spores that had clumped together. Two animals lived just a little less than twenty days. Seven lived between twenty and thirty days; two between thirty and forty days; two between forty and fifty days; four between fifty and sixty days, and four between sixty and sixty-five days.

The kidneys, i. e., the injected kidneys, of the animals in this series showed, in general, uniform findings. Leaving out the presence of large infarcts, due to faulty technic or obstruction of large branches of the renal artery by masses of spores, the kidneys showed, grossly, a varying amount of pitting or coarse depressions, with wedge-shaped cortical scars. Microscopically, wedge-shaped areas were found in the cortex, with relatively wide bases, in which were seen tubular degeneration, atrophy and distortion; marked fibrosis between the tubules and around the glomeruli; often large masses of round cells near a vessel containing spores and an organized, canalized thrombus, and a varying number of spores in the arterioles, very rarely in a glomerulus. The spores were just large enough to obstruct the afferent vessel of the glomerulus, but too large to get in the capillaries. Between these areas of scarring, little change was evident, other than the focal scars of spontaneous nephritis, which could be distinguished only with great difficulty from those due to the spores and bacteria. In fact, in many instances, only the finding of spores in the vessels was the differential point. In some kidneys, the findings were frankly those of multiple organized or organizing infarcts, with tremendous interstitial fibrosis. Within these areas, the glomeruli themselves showed little or no change, even in cases in which a spore was present in the glomerular capillary. Pericapsular fibrosis was marked.

All these changes could be attributed to partial or complete obstruction of arteries to the involved areas. In other words, this was a focal embolic process, the obstruction being due to the inert spores. The bacteria apparently played no important rôle—not any more than in Series 2, in which organisms and diphtheria toxin were injected into the rabbits. The only lesion that could be attributed to bacteria was the

tremendous focal lymphocytic accumulation seen about some of the small vessels in the cortex and sometimes in connection with a glomerulus. This lesion was not seen in a rabbit which had received only spores in sterile physiologic sodium chlorid solution, although the usual scarring was present.

While one could not tell, in the case of the left kidney, how much of the pitting was due to the treatment and how much was spontaneous, the analysis of the findings in the opposite, untreated, control right kidney gave interesting results. Fourteen of the twenty-six rabbits showed a varying amount of gross pitting, in the right kidney. Three more showed microscopic scars and round-cell infiltration—making a total of seventeen of twenty-six which had spontaneous nephritis, unless the findings could be attributed to the effect of circulating bacteria, originally injected into the opposite kidney. But this explanation could not possibly hold for the extreme scarring and puckering of the kidneys of two rabbits that died during the operation. Nor could it explain the pitting found in the right kidney of the rabbit which received only spores. Whatever the cause of the pitting in the right kidneys, the incidence was unusually high in this series.

The bacteria injected into the left renal artery produced a definite vegetative endocarditis in four rabbits, which lived five, eighteen, nineteen and twenty-seven days, respectively. In the first animal, there were microscopic embolic abscesses in the myocardium. In the second animal, there were focal leukocytic infiltration in the myocardium and an infarct in the right, or untreated kidney.

6. During the course of the various experimental procedures carried out above, a simultaneous study was made of the histologic condition of kidneys obtained from rabbits which happened to die in the laboratory. Some were unused rabbits, supposedly normal. Most of them had been injected with human serum, lens protein, etc., in the course of work on precipitins. None had received bacteria of any sort.

A total of eighty-two kidneys (forty-one rabbits) were studied. Forty-eight kidneys (twenty-four rabbits) were entirely normal; thirty-four showed a varying amount of focal cortical scarring, round-cell infiltration, etc. In many of the thirty-four, gross pitting was present. Thus, more than 40 per cent. of these rabbits showed spontaneous nephritis. This is an important phase of the work on experimental nephritis in the rabbit.

V. SUMMARY

A critical, yet, we trust, a fair review of the literature on experimental chronic glomerulonephritis shows that many investigators have reported successful results that cannot stand when viewed in the light of strict criteria for glomerulonephritis. But many who have made

careful and extensive experiments have failed completely to produce chronic renal lesions comparable to the typical chronic glomerulonephritis of man. Not all the workers have seemed to distinguish between "spontaneous" nephritis and the true form of chronic glomerulonephritis which ends in the so-called granular or contracted kidneys.

The present attempt to produce glomerulonephritis, by injection of bacteria repeatedly, of bacteria and diphtheria toxin, of bacteria and snake venom, of bacteria and spores directly into the renal artery, has met with absolute failure. Many pathologic processes have been described in the protocol, but none of these is a true glomerulonephritis. Yet the bacteria were able to produce vegetative endocarditis (never ulcerative) in a fair proportion of the animals.

"Spontaneous" nephritis was found in 40 per cent. of rabbits which had never received bacterial injections. In seventy-two of 133 rabbits used in the experiments of this research, spontaneous nephritis was noted, whether spontaneous or not cannot be decided. In other words, 54 per cent. had the typical lesions, which, however, are very easy to distinguish from those of glomerulonephritis.

VI. CONCLUSION

Chronic glomerulonephritis has not yet been produced constantly or even frequently in an experimental animal. The rabbit is probably not a suitable animal for this purpose, because it does not react as does the human being to the agents that can injure the glomeruli. My own attempts to produce a chronic lesion by means of bacteria alone, bacteria with diphtheria toxin, bacteria with snake venom or bacteria with spores, all calculated to damage the circulation within the glomeruli and introduce infection at the same time, have been unsuccessful, although a large number of animals were used with each method of procedure. Whatever changes were observed in the kidneys could not be interpreted as those of chronic glomerulonephritis.

HEMATOPORPHYRINURIA AS AN INDEPENDENT DISEASE ("HEMATOPORPHYRIA") AND AS A SYMPTOM OF LIVER DISEASE AND INTOXICATIONS *

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Among the so-called autointoxications, there is a group, not very well defined, characterized by a constitutional defect which prevents the complete decomposition of certain substances. As a result, intermediate metabolic products accumulate in the blood and internal organs, and at times well defined morbid conditions, even death, may result.

Such conditions have long been known, among them being arthritis urica, diabetes mellitus, the comparatively unimportant cystinuria and alkaptonuria. The last named condition is now well known, chiefly since the appearance of a monograph by the Danish investigator Valdemar Poulsen.[1] Its sequel, ochronosis (blackening of cartilage and other tissues), had already been described by Virchow, and, on account of its rarity and harmlessness, may be considered a pathologic curiosity.

Of greater practical and theoretical importance is hematoporphyrinuria, so named on account of the presence in the urine of a light reddish brown pigment, best known to occur in connection with poisoning by sulphonmethane and sulphonethylmethane. Less known is the fact that hematoporphyrinuria may be the expression of a constitutional state, "porphyria," or "hematoporphyria," an exceedingly interesting condition with a fairly well defined morbid anatomy, and recently the subject of a monograph by Hans Günther.[2]

REPORT OF CASES

CASE 1.—*History.*—A hostler, aged 43, had been under the observation of Prof. Peter Bull for many years. In 1903, when 28 years old, he had two months of diarrhea with rather scanty, painless and at times bloody stools. This was followed by constipation. There was no jaundice. The following year he was in bed a week with fever, vomiting and pain in the right hypochrondriac region, radiating to the back. He had a similar attack in 1905, and was never entirely well, being frequently troubled with nausea, poor appetite and pain in the right side. In 1906 and again in 1910, he had similar attacks. In 1910, it was noted that the urine was dark, with light colored foam, and free from sugar and bile pigments. The addition of iodin caused it to be more intensely brown (not green). Nov. 3, 1910, laparotomy was performed and the appendix was removed. The biliary tract was normal. Nine days later, he had an attack of pain during which the urine was dark and contained urobilin and hematoporphyrin. The action of the bowels was normal.

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* From the Department of Pathology, University of Christiania.

1. Poulsen, Valdemar: Om ochronotiske tilstande hos mennesker og dyr, 1910.

2. Günther, Hans: Die Bedeutung der Haematoporphyrine in Physiologie and Pathologie, 1922.

November 15, the muscular power in the arms was much reduced and the grip weak, and there was distinct atrophy of the thenar eminences. Sensation was normal. The abdomen was constantly tender.

November 23, on neurologic examination by Dr. Eyvin Krogh, evenly distributed paresis of both arms and legs was found. The tendon reflexes were absent; sensation was normal; the eye grounds were normal; the urine was yellow. Retention of urine was present for a month, and the weakness of the extremities lasted a year. It was thought that there was an acute affection of the anterior horns or roots of the cord, extending at least as high as the fifth cervical segment, the cause being an intoxication or infection.

Further Observations (Dr. Andreas Tanberg).—From 1911 to 1913, the patient improved considerably, and he became able to walk about by the aid of a cane. In the fall of 1916, he grew weaker, and in March, 1918, he was confined to bed. He complained of pain here and there in the arms and legs. Once or twice a year, he had peculiar attacks of abdominal pain, lasting about a week, and less severe in recent years. The onset was usually sudden, and the pain was usually in the umbilical region. The patient had the impression that the pain started on the right side. There was no distension, and tenderness was not pronounced. The pains, which were stinging and burning, were usually accompanied by vomiting of watery and, toward the end, bile-stained material. The urine was of light color on the first day of the attack, but grew darker from day to day and the dark color, the shade of Madeira wine, persisted for several days after the cessation of pain. The temperature was always normal, the pulse rate from 80 to 100. The skin and sclerae were slightly icteric during the period of excretion of dark urine.

During one of the attacks in 1911, there was tenderness and swelling of both breasts, and the lightest touch of the nipples caused pain. The liver was not enlarged during the attacks. Spectroscopic examination of the urine revealed large quantities of urobilin and urobilinogen, together with a trace of hematoporphyrin. In the later years, the skin and sclerae were constantly slightly yellow. In 1916, he began to have frequent attacks of vertigo, with vomiting and sometimes fainting. The same year, there appeared a slight paresis of the muscles of the right side of the face. Signs of chronic nephritis were present during the last five or six years of his life, the urine containing from 0.5 to 1 per cent. of albumin, granular and hyaline casts, a few leukocytes and a very few erythrocytes. During the last eighteen months, albuminuric retinitis had been present.

The patient had used alcohol only moderately. In 1910, a negative Wassermann reaction was obtained.

Outcome.—April 16, 1918, the patient was admitted, in a comatose condition, to the service of Prof. Peter F. Holst. A week previously, one of his usual painful attacks had come on, and from day to day, consciousness became more clouded. There was no fever, but the pulse rate was 120. The area of cardiac dulness was slightly increased. Atrophy of the musculature of the hands, forearms and legs was noted. The urine contained a considerable quantity of albumin and casts. The patient died April 18.

Necropsy Findings (April 18).—The body was that of a man who appeared older than his chronological age. There were numerous punctate hemorrhages on the radial side of the right forearm. The musculature of the thenar and hypothenar eminences, forearms and legs was considerably wasted. The pericardial cavity contained clear yellow fluid, and its layers were smooth. The heart was enlarged, weighing 450 gm., and the wall of the left ventricle was thickened and its cavity dilated. There were a few sclerotic patches in the coronary arteries, but no narrowing of their lumen. Otherwise, the heart was normal. The pleural cavities were normal as were the lungs, aside from slight hypostatic congestion. There were some fibrous adhesions about the gallbladder. The spleen was enlarged, weighing 135 gm., and rather firm, and its follicles

were indistinct. The kidneys were also rather large with adherent capsules and presented, on cut surfaces, numerous cysts and yellow patches. The line of demarcation between cortex and medulla was entirely effaced. The liver was rather small, weighing 1,100 gm., and somewhat cyanotic, with indistinct markings. The gallbladder and ducts were normal. The stomach, intestines, pancreas and bladder showed no changes. The skull and dura mater were normal. The brain was large and edematous, with broad gyri and narrow sulci. The vertebral arteries were thickened and tortuous, with sclerotic patches in their lining. The basilar artery was still more dilated and also sclerotic, with a thrombotic mass which almost filled the lumen in its lower portion. Corresponding to the thrombus, there was softening in the lower portion of the pons. There were also small foci of softening on the right side of the cerebellum, at the tip of the left caudate nucleus and in the wall of the third ventricle. The small arteries at the bottom of the cerebral sulci were sclerotic. The spinal dura presented in the cervical region a fibrous thickening up to 3 mm. of the consistency of scar tissue, as well as brownish pigmentation. The cord itself was slightly swollen in the cervical region and the demarcation between the gray and the white matter was not distinct. The white matter appeared somewhat degenerated. The same was true to a less degree of the rest of the spinal cord.

Histologic Examination.—Kidneys: There was marked degeneration of the epithelium of the convoluted tubules, which was partly shed. The lumina of the tubules were narrow in places, in other places dilated, and partly filled with homogeneous material. The stroma was considerably increased in both the medulla and the cortex; in the latter, this occurred in areas in which the epithelium was much degenerated and partly destroyed. There was some round-cell infiltration in the cortex, and the glomeruli were largely converted into hyaline lumps in which degenerated nuclei were seen. The walls of the larger vessels were somewhat thickened.

Liver: This showed parenchymatous degeneration.

Brain: In the cortex of the cerebrum, as well as in the underlying white matter, there was abundant yellowish brown granular pigment around both veins and arteries. The brain tissue was edematous, most distinctly so about the vessels. Yellow pigment was also found in the meninges. These findings were less marked in the basal ganglions, and scarcely recognizable in the cerebellum. There was no sign of inflammation anywhere and no marked change in the ganglion cells. The arteries of the base, especially the basilar artery, showed considerable intimal proliferation with slight cell infiltration, considerable pigmentation in the deep portion of the wall and deposits of lime salts. There was a conspicuous swelling from edema of the vascular walls, with a reticular appearance, and, in other places, hyaline degeneration was present. There was practically no inflammatory change about the vessels.

Spinal cord: The changes were not marked. There was no inflammatory infiltration in either the membranes or the cord substance. Slight edema was present in the cervical region but not elsewhere. The ganglion cells were normal, except for questionable atrophy of portions of the anterior horns in the upper cervical region.

Peripheral nerves: The sciatic, ulnar and radial nerves gave no evidence of inflammation, but there was some granular degeneration of the myelin sheaths and axons. Marchi preparations were not made.

Anatomic diagnosis: Porphyrinuric autointoxication (?); chronic nephritis with atrophy; hypertrophy of the heart, chiefly of the left ventricle; arteriosclerosis, particularly of vertebral and basilar arteries; thrombosis of the basilar artery; softening of a portion of the cerebellum and pons, wall of third ventricle and left caudate nucleus; edema of the brain; myelitis of cervical region of cord (?); spinal pachymeningitis with pigmentation; atrophy of the musculature of the upper and lower extremities, and parenchymatous degeneration of the liver.

Comment.—The findings in this case agree quite well with those described during the past ten years as porphyrism or hematoporphyria acuta. About twenty cases have been reported, and most of them are assembled in the previously mentioned monograph by Hans Günther. Recently, additional cases have been reported by Snapper.[3] The acute form of the disease has affected women in about two-thirds of the cases, and in about one-third of the cases there has been a neuropathic or psychopathic basis. There is a triad of symptoms, consisting of intestinal colic, vomiting and obstinate constipation. Attacks of abdominal pain occur without demonstrable reason. The pain usually begins in the epigastrium and often radiates to the loins or to the lower extremities. Epigastric tenderness may be present. Vomiting occurs in 90 per cent. of the cases. The clinical picture may thus resemble appendicitis, gallstones, kidney stone or ileus. There is usually retention of gastric contents, with dilatation of the stomach and upper part of the small intestine; in other words, symptoms pointing to partial obstruction in the intestine, which has been interpreted as spasm of the duodenum or upper ileum. We may also see the picture of acute dilatation of the stomach or duodenum. The vomitus is often bile-stained. To this condition is added obstinate atonic constipation, with small lumpy stools and bloody mucus. Vesical tenesmus may occur. Fever has been present in half of the cases.

The blood examination reveals normal conditions. The blood serum does not, as a rule, contain hematin or hematoporphyrin, and there are no signs of hemolysis.

The characteristic feature is the abnormal condition of the urine during the attack. It assumes a reddish brown, port wine or malaga color, and, on spectroscopic examination, it is found to contain hematoporphyrin, namely, uro- and enterohematoporphyrin. Urobilin and urofuscin may be found in the urine, which usually is very acid and scanty. In one-third of the cases, albumin and casts have been found. Sugar, hemoglobin, hematin and bilirubin are not present.

The attacks mentioned usually occur several times a year, as in Case 1. A whole series of nervous symptoms gradually appear: sensory disturbances, neuralgic pains, insomnia, the presence of hyperesthetic zones, psychoses, epileptiform attacks, deliria and, finally, mild polyneuritic symptoms, such as radial or ulnar palsy with tenderness of these nerve trunks. Complete paralysis and sometimes amaurosis may develop. Ascending paralysis has been described in about 50 per cent. of the fatal cases. Toward the end, in addition to paralysis of the extremities, paralysis of the sphincters, vocal cords and ocular muscles may set in, and the tendon reflexes disappear. Death usually occurs a few weeks after the onset of an acute attack.

3. Snapper, I.: Deutsch. med. Wchnschr. **48**:619 (May 12) 1922.

The postmortem findings have been relatively few and ill-defined. There has usually been degeneration of the liver with "siderosis." The bile is dark. In the kidneys, there are usually fatty degeneration and hyperemia. Chronic nephritis was found in one instance. Brownish red granular pigment is found in the epithelium of the renal tubules. Degeneration of the pancreas has been described, and in the stomach and intestine, erosions and hyperemia. In the large intestine, coating with mucus and pus has been found. Siderosis of the spleen sometimes is present.

The greatest attention naturally has been given to the nervous system, both central and peripheral; but as yet the findings have been few, inconstant and indefinite. There seems to be agreement on the absence of inflammatory alterations. Marked and widespread degeneration of the ganglion cells of the anterior gray horns of the cord and spinal ganglions has been met with, though relatively seldom. In other cases, there have been degeneration of peripheral nerves and corresponding muscular atrophy.

As to the deposition of hematoporphyrin in the tissues, there has been practically no investigation which would be of interest, particularly in connection with cartilage and bone.

The findings in our own case contain many points of interest, particularly in the absence of inflammation and degeneration of brain and cord cells; while the presence of parenchymatous degeneration of nerve fibers points to such nerve degeneration as the cause of the marked muscular atrophy encountered. Of further interest is the pigment deposit in the walls of the cerebral vessels and in the membranes of the spinal cord, the latter associated with fibrous thickening of the dura in the cervical region.

The second group of changes which dominates the anatomic picture consists of the severe arteriosclerosis and nephritis. The arteriosclerosis was general, but most pronounced in the brain, where it led to dilatation and secondary thrombosis of the basilar artery, which was the immediate cause of death. I consider it reasonable to suppose that the arteriosclerosis is part of the disease, as there was pigmentation as well as proliferation in the arterial walls and because arteriosclerosis is a prominent feature of other autointoxications. I have previously pointed this out in connection with affections of the parathyroids, abnormal calcification and osteomalacia.[4]

The chronic nephritis with atrophy should also be looked on as a link in the disease. Both it and the arteriosclerosis are the expression

4. Harbitz, Francis: Pathologiske fund i hypofysen og glandulae parathyreoidea, 1916; Et tilfälde av osteomalaci med svulst av gland. parathyreoidea, 1915.

of a long continued effect on the tissues of injurious toxic substances.[5] The liver degeneration is probably also of great importance for the whole clinical picture.

In acute cases, the clinical picture, as well as the anatomic findings, may be quite different. Through the kindness of Dr. N. B. Gröndahl, I am able to relate the following case, observed by him nearly twenty years ago:

CASE 2.—*History.*—A woman, aged 27, a robust domestic, admitted to the Stavanger Hospital, Dec. 31, 1904, about December 15 had complained of fatigue and loss of appetite. This was followed in a few days by pain in the right iliac fossa, and within a week by severe pain under the left costal arch, with some tenderness. December 30, she had a sudden attack of unconsciousness with clonic spasms, dilated pupils, and opisthotonos. A similar attack occurred the following night. Between the attacks, she was stuporous and did not respond to questioning.

Examination.—On admittance, she was rather restless, with a pulse of 140, and with some general impairment of sensibility. There was no trace of paralysis. The urine was yellowish red, and the coloring matter could not be extracted by chloroform.

Course.—Jan. 1, 1905, there were five attacks of unconsciousness, the first four very brief, the fifth one of fifteen minutes' duration, with clonic spasms of the right half of the body. January 4, she was very restless and had hallucinations of sight. Hypnotics were required to produce sleep. Fever was present. January 8, she was very dull and had involuntary discharges. The urine, which was dark brownish red, contained no albumin, sugar, or blood. January 13, the urine had become Burgundy red. The patient was very weak and pale, and, January 15, she became cyanotic and completely apathetic. The blood serum was not discolored. Cheyne-Stokes breathing developed, and she died, January 16. Urine obtained during the last few days of life was sent to the Physiologic Institute, and Professor Torup reported that it contained "hexahydrohematoporphyrin, a reduction product of hematoporphyrin produced by liver degeneration."

Necropsy (Dr. Gröndahl).—The meninges and brain were normal. Hemorrhages were seen in the epicardium and beneath the endocardium on the right side. The heart was soft and small. The lungs were normal. The liver was small and very soft, almost mushy. The cut surfaces were yellowish brown with indistinct markings. The spleen, kidneys, stomach, intestines and genitalia showed no gross changes.

Histologic examination of the liver revealed degeneration of all liver cells, and there were numerous yellowish brown pigment granules, especially in the peripheral portions of the acini and in the vessels. The epithelium of the biliary tract was normal. A diagnosis of subacute liver degeneration was made. In the kidneys, there was degeneration of the cortical epithelium and in both cortex and medulla the epithelium and interstitial tissue contained numerous pigment granules similar to those seen in the liver.

Comment.—The striking feature of this case was the early appearance of cerebral symptoms which evidently depended on the hepatic disease. The abnormal condition of the urine was first observed at about the middle of the disease, the urine gradually growing darker

5. Recently, Kleinschmidt (Frankfurt. Ztschr. f. Path. **28,** 1920) reported a case of endogenous ochronosis with alkaptonuria, in which both arteriosclerosis and chronic nephritis existed.

on account of the presence of hematoporphyrin. It is reasonable to consider the hematoporphyria as a symptom of the whole disease, particularly of the liver affection. In many ways, this case differs from other cases of hematoporphyrinuria. Anatomically, it most closely resembles acute yellow atrophy. The cause of the disease is obscure.

In addition to the idiopathic constitutional form we have an acute toxic hematoporphyria. This is best known as occurring after the prolonged use of sulphonmethane, and has been most frequently observed in women. However, as only a few patients taking this drug develop hematoporphyrinuria, we must assume a special predisposition, probably dependent on physical and mental depression. Serious cases have been observed after the ingestion of from 10 to 20 gm. The symptoms resemble those described for the idiopathic form, with the triad of intestinal colic, vomiting and constipation. Later, pigmentation of skin and mucous membranes is observed. Most characteristic, of course, is the condition of the urine such as has been described. Nervous symptoms, as neuralgic pains, paresthesias, palsies, and sometimes terminal ascending paralysis make their appearance. The mortality, according to Günther, is 90 per cent., but this figure is probably much too high. The duration has varied from four to ten days. Anatomically, degeneration and pigmentation of the liver have been found, sometimes also swelling and pigmentation of the spleen, toxic neuritis and scattered degenerations in the central nervous system. The manner in which sulphonmethane produces hematoporphyrinuria is not known.

Following is a case of this kind, but with urobilin in the urine:

Case 3.—*History.*—A woman, aged 21, was admitted to a hospital in May, 1908, with a diagnosis of hysterical insanity. At the age of 16 she had been treated for an abdominal disease, probably tuberculous peritonitis. Later, she developed obstinate diarrhea and cystitis, with foul urine. For a time, albuminuria was present, disappearing in March, 1904. Later, the patient was troubled with constipation, dyspeptic symptoms and, a few times, vomiting of blood. She often complained of headache, and for seven or eight years, she had been subject to attacks of hysterical laughing and crying. During an attack of restlessness with hallucinations in March, 1908, she had been given barbital on fifteen occasions. May 6, she was admitted to another hospital where she was given barbital, sulphonmethane, paralydehyd and hyoscin. On account of the appearance of a morbilliform eruption, barbital was discontinued. May 16, the urine became red, and hematoporphyrinuria was suspected, but Professor Torup found the abnormal substance to be urobilin. The patient became apathetic, and developed slight fever with sluggish pupils and loss of knee reflexes. Otherwise, there were no definite physical signs. She died, May 22. During the period from May 16 to 18, she had taken a total amount of 10.5 gm. of sulphonmethane, 1.5 gm. of barbital, 10 c.c. of paraldehyd, and about 2 mg. of hyoscin. No hypnotic was given later than May 19. The urobilinuria lasted seven days.

Necropsy.—There were no changes of the skin, meninges, brain, heart or lungs. The liver was small (820 gm.) soft and dark, with a yellowish green olive-like tinge, with dark and indistinct markings. The bile ducts were normal. The spleen was also small (80 gm.), rather dark and soft. The kidneys weighed

200 gm., and were firm with adherent capsules, indistinct markings and closely set yellow stripes in the cortex. The urinary bladder was normal. There were old adhesions about the ovaries and tubes, but no signs of active tuberculosis. The stomach and intestines were normal.

Histologic examination of the motor area of the brain revealed no definite changes. The peripheral nerves were not examined.

The main feature was the liver degeneration, which was in a stage of transition to acute yellow atrophy. The chronic nephritis is also of importance.

Similar cases of poisoning have been observed after prolonged use of sulphonethylmethane. Eleven cases have been reported. Chronic lead poisoning also has been considered a cause of hematoporphyrinuria, and the presence of urobilin in blood and urine, pigmentation of the skin, cirrhotic changes in the viscera, colic and polyneuritis are recognized features of lead poisoning. In a recent study of industrial lead poisoning a Danish physician, Tage Plum [6] found hematoporphyrinuria to be very frequent. In control examinations of seventy other patients, Plum found hematoporphyrinuria in one case of cirrhosis with marked icterus, and in a patient with hemolytic icterus.

Among other poisons said to have caused hematoporphyrinuria are barbital, phenobarbital, acetanilid and nitrobenzene.

An interesting case of hematoporphyrinuria ascribed to chloroform was reported from Norway in 1901 by Johan Nicolaysen.[7]

CASE 4.—*History.*—A woman, aged 29, came to the hospital in January, 1900, with supposed appendicitis. The urine was dark yellowish brown, of specific gravity, 1.039; contained no albumin, sugar, bile pigment or blood, and gave a red ring with Heller's test. The patient was discharged as recovered in a few weeks, but some days later she complained of pain in the back and right iliac fossa. In April, she had a sudden attack of epigastric pain with intestinal colic, vomiting and constipation, and no particular tenderness at McBurney's point.

Operation and Course.—May 1, the appendix was removed, and was said to show signs of chronic appendicitis. The next day, the urine was reddish brown, of specific gravity 1.035, and contained hematoporphyrin. The patient recovered promptly. Four months later, the urine was reddish yellow and acid, of specific gravity 1.026, and contained urobilin. In October, 1923, Professor Nicolaysen reexamined the patient and learned that she had had no more colic or constipation, but that the urine had remained dark for many years. Until ten years ago, she had frontal headache, with vomiting every week, and during these attacks, the urine was usually dark. Now the urine was light yellow, of specific gravity 1.015, and contained no albumin, sugar or pus.

Comment.—It is reasonable to assume that this was a mild case of hematoporphyrinuria and that the alleged appendicitis really was an attack of the former. The chloroform narcosis appears to have rendered the hematoporphyrinuria manifest. Noteworthy is the subsequent transition to urobilinuria and the good state of health of the patient in later years. We may here have a porphyria with good

6. Plum, Tage: Nord. Hyg. Tidskr. **2**:191, 1921.
7. Nicolaysen, Johan: Norsk. Mag. f. Lægevidensk. **24**, 1901.

prognosis, a condition of which we know almost nothing, but which may be more common than we think.

A chronic form of hematoporphyria has been described, but it is rare and even of doubtful identity. It is familial and congenital, becoming manifest in late childhood or at middle age and occurring in paroxysms with long or short intervals, often with intestinal prodromes. It is particularly characterized by cutaneous lesions after exposure to light. These consist of erythemas, vesicular formations, often marked pigmentation, and typical *hydroa aestivale* or *vacciniforme*. Some hours after exposure to light, especially in spring or summer, there appear on the unprotected portions of the face and hands, the sensation of heat, itching and formation of vesicles, sometimes with bloody contents. Coryza, conjunctivitis, edema and diarrhea may be associated, the attack usually lasting from two to five days, during which time the urine becomes reddish brown and contains hematoporphyrin. The cutaneous symptoms have been ascribed to deposition of hematoporphyrin in the skin. Subsequently, the skin may remain thickened, the condition resembling scleroderma.

Thirteen cases have been reported as congenital hematoporphyria. They were characterized by repeated attacks of eruption after exposure to light, with associated hematoporphyrinuria, as well as the presence of urobilin and urofuscin in the urine. Pigmentation, erythemas and vesicle formation, even with pus, occur, and subsequently, cicatrix formation and mutilation of the nose, eyes, ears and fingers. The latter become atrophic, often ankylosed, with deformed nails, and whole phalanges may be lost. Hence, the affection may closely resemble leprosy or syringomyelia. It is said that the disease, in part, occurs when the patient is neuropathic, and in individuals with a tendency to pigmentation and strong growth of hair. The eyes may be the seat of yellowish pigmentation, severe conjunctivitis and, later, keratitis and iritis, with resulting ulceration, leading to blindness. Enlargement of the spleen may exist, but symptoms on the part of the nervous system are lacking, and the blood picture is normal. Anatomically, we may find a large, brownish red spleen with abundant pigmentation, as well as a cirrhotic and pigmented liver, while the kidneys are free from pigment. Pigmentation is also found in the bones and the cement of the teeth, especially in a case reported by Hegler, E. Fränkel and Schumm.[8] The cranium, sternum, and ribs were brown, the cartilages white.

AFFECTION OF ANIMALS

In otherwise healthy cattle, horses and hogs, a condition has been described which seems to be identical with, or at least closely related

8. Hegler, Fränkel and Schumm: Deutsch. med. Wchnschr., 1913, p. 18.

to, human hematoporphyria. This is the so-called ochronosus characterized by reddish brown or chocolate brown discoloration of the bone tissue. The cartilage is not involved, while in human beings the reverse is true, the cartilage being blackened while the bones are normal. The color depends on deposits of substances one of which, according to the chemical and spectroscopic properties, is hematoporphyrin. The condition is rare and has not been closely studied. To my knowledge, no case has been observed in Norway. Alexandra Ingier,[9] while working with Schmorl in Dresden, studied the affection in an ox and a hog, and found a pigment which proved to be a hematoporphyrin. She looks on ochronosus as a metabolic disorder dependent on certain enzyme activities.

GENERAL COMMENT

The essential feature being the presence of hematoporphyrin in the urine, we will describe this substance in further detail. When produced artificially from hematin, it is reddish violet, but if in a strongly acid solution, it is of a purple hue. It is insoluble in water and weak acetic acid, sparingly soluble in ether and chloroform and soluble in alcohol, in dilute acids and alkalis. In glacial acetic acid, it dissolves with formation of thin, rhombic, reddish brown crystals. It has no definite chemical reactions, but a typical spectroscopic picture. To observe the latter, it is customary to extract with alcohol containing a little hydrochloric acid, or by shaking the urine with equal parts of acetic ether with addition of a little 30 per cent. acetic acid (Saillet's method). In legal medicine, spectroscopic examination for hematoporphyrin is used in the examination of suspected blood stain in decomposed material, extraction with concentrated sulphuric acid for fifteen or twenty minutes being employed. We do not as yet know what hematoporphyrin really is and where and whereof it is formed. It is generally thought that it is formed from hemoglobin by the splitting off of the iron, for it is free from iron. Its chemical formula is generally given as $C_{16}H_{18}N_2O_3$ or $C_{34}H_{38}N_4O_6$. Experimentally, it is readily prepared by treating hematin with hydrobromic acid and glacial acetic acid, and this is the "porphyrin" the solutions and spectrum of which are described in technical works.

It was thought that this "genuine" hematoporphyrin was identical with the coloring matter found in the urine in the diseased condition described by us, but the matter is not so simple. We have gradually learned that there are several porphyrins: in addition to the artificial one, a urohematoporphyrin and an enterohematoporphyrin or coprohematoporphyrin are found in the urine in this disease. The last named substance can be obtained also from the stools when much blood

9. Ingier, Alexandra: Ziegler's Beitr. **25**:199, 1911.

is given in the food as it forms during the decomposition in the intestine, but it is not absorbed and does not seem to play any important rôle (Hans Fischer [10]).

What is the source of the porphyrin found in the urine and blood in the disease porphyria? There is apparently no destruction of red cells with decomposition of their coloring matter, and hematoporphyrinuria does not occur in connection with hemolysis nor in hemoglobinemia or hemoglobinuria. While there is no direct decomposition of hemoglobin or transformation of it or hematin to hematoporphyrin, there is every reason to believe that hemoglobin is its source.

Nor are the porphyrins likely to be formed in the intestinal canal, absorbed in the blood, and excreted in the urine. They must be due to endogenous formation in the body cells, but we do not know in which ones. It is natural to think of the liver as the place of formation, especially as pronounced disease of this organ has been demonstrated (as in our Cases 2 and 3). The frequent simultaneous appearance of urobilinuria supports this view, as it is considered a sign of hepatic insufficiency. This intimate association between the two substances was shown in our Case 4; in which urobilinuria followed hematoporphyrinuria. It has been thought that bilirubin may furnish material for hematoporphyrin (hydrobilirubin resembles urobilin and is isomeric with it), but we know nothing about it. Recently, the muscle pigment, myohemoglobin or myohematin, has been thought of as a source, but its genesis also is not clear. However, by the action of sulphuric acid, a porphyrin may be split off from it.

We are also in ignorance in regard to the toxic hematoporphyrinuria in poisoning with sulphonmethane, sulphonethylmethane and lead, but the genesis is probably the same as in the idiopathic form.

As has been stated before, a special disposition seems essential, a reduced mental and bodily vitality. Greatly increased breaking down of muscle substance may be a factor. As regards the pathogenesis, we may assume that the hematoporphyrins have a toxic action and produce degeneration in the nervous system and possibly also arteriosclerosis and chronic nephritis.[11] This is supported by certain experimental data, but it is not by any means proved. It must in particular be remembered that the congenital form is not associated with actual toxic phenomena, but with a photosensibilization.

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10. Fischer, Hans: München. med. Wchnschr. **70**:1143 (Sept. 7) 1923.

11. Snapper (Footnote 3) has recently claimed that the symptoms in this disease are produced by pressure on the retroperitoneal nerve plexuses (in one of his cases, by tuberculous glands, and in another by a hydronephrosis), resulting in hemorrhagic erosion of the stomach, intestinal colic, and an injurious influence on the liver, and formation of hematoporphyrin. This however, seems to me improbable as demonstrable abdominal lesions, which might have such injurious influence on the nervous system, are usually lacking.

CALCIUM TREATMENT FOR EDEMA*

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Meyer and Cohn,[1] in 1911, studied the effect of various salts on the weight and mineral balance in normal infants. They found that by giving calcium salts they could cause a decrease in weight due to water loss. In the case of calcium chlorid, they found that the calcium ion seemed to be largely excreted in the stool, while the chlorin ion was excreted in the urine in combination with other bases.

Schultz,[2] in 1918, reported ninety-three cases of war nephritis which he had observed and treated. On the basis of the work of Meyer and Cohn, he tried the effect of large doses of calcium chlorid, and in many instances the edema disappeared completely. The calcium was not always effective, however. In certain of the resistant cases, there was apparently also a cardiac factor, and occasionally a combination of digitalis and calcium produced diuresis and loss of edema fluid.

Hülse,[3] in 1920, reported eight cases of war nephritis with edema treated successfully by doses of calcium chlorid of from 15 to 20 gm. a day. He believed that the calcium in some manner freed the sodium chlorid and water that were held by the tissue colloids. He emphasized the fact that, besides the reduction of the edema, renal function improved definitely.

Blum [4] and his colleagues, in studying the action of various diuretics

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* Work done in the Division of Medicine, Mayo Clinic.

1. Meyer, L. F., and Cohn, S.: Klinische Beobachtungen und Stoffwechsel Versuche über die Wirkung verschiedener Salze beim Säugling, Ztschr. f. Kinderh. **2**:360-419, 1911.

2. Schultz, E.: Klinische Beobachtungen über Nierenentzündung bei Kriegsteilnehmern, Ztschr. f. klin. Med. **86**:111-138, 1918.

3. Hülse, W.: Ueber den Einfluss der Kalksalze auf Hydrops und Nephritis, Zentralbl. f. inn. Med. **41**:441-454 (June 19) 1920.

4. Blum, L.: Le traitement des affections inflammatoires des séreuses par le chlorure de calcium, Presse méd. **30**:221-225 (March 15) 1922. Blum, L.; Aubel, E., and Hausknecht, R.: L'action diurétique des sels de calcium dans les oedèmes généralisés. Mécanisme de cette action, Bull. et mém. Soc. méd. d. hôp. de Paris **45**:1561-1569 (Nov. 25) 1921; Action diurétique des sels de calcium. Mécanisme de cette action, Compt. rend. Soc. de Biol. **85**:950-952, 1921; Modification de la composition minérale du sang et des humeurs après ingestion de chlorure de calcium, Compt. rend. Soc. de Biol. **85**:1159-1162, 1921; L'action diurétique des sels de calcium dans la néphrite avec oedemes, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:206-214 (Feb. 3) 1922. Blum, L.; Aubel, E., and Lévy, R.: L'action diurétique des sels de potassium dans les épanchements ascitique et dans les oedèmes dits essentiels, Bull. et mém. Soc. méd. d. hôp. de Paris **45**:1504-1513 (Nov. 18) 1921. Blum, L., and Bang, O.: L'action diurétique des sels de calcium dans l'ascite de la cirrhose du foie, Bull. et mém. Soc. méd de hôp. de Paris **45**:1569-1572 (Nov. 25) 1921. Blum, L., and Schwab, H.: L'action du chlorure de calcium dans les hydropsies cardiaques, Bull. et mém Soc. méd. d. hôp. de Paris **46**:214-220 (Feb. 3) 1922.

on edema, in 1921, found that large doses of potassium salts (10 gm. a day) reduced edema. Fearing the toxicity of these salts, they turned to calcium, and found that they could substitute 10 gm. a day of calcium chlorid with equal benefit. They secured very good results in causing a disappearance of the edema of nephritis and of the idiopathic edema of the nephrosis type. No benefit was obtained in cases of edema of cardiac origin; in fact, a few of the patients became worse. In ascites due to cirrhosis of the liver, and in pleurisy with effusion, the amount of fluid was diminished, or removed entirely in certain cases. Blum and his associates studied the electrolytes in the urine, and found that the calcium apparently caused increased excretion of sodium. When the sodium ion was retained, water was retained with it; when it was excreted, diuresis occurred. These observers also found that calcium did not produce good results unless the patient was on a diet that was also low in salt, and that giving both calcium and sodium chlorid produced little change. These conclusions have been confirmed in part by the work of Brelet [5] and Krummenacher.[6]

Atchley, Loeb and Benedict [7] studied the electrolytic partition in the blood and urine in a case of diabetic edema under treatment with calcium chlorid. They also found that the chlorin ion was largely excreted in the urine as the ammonium salt. The excretion of the sodium ion in the urine was markedly increased, while the excretion of the calcium and potassium ions was only moderately increased.

Haldane, Hill, and Luck [8] tried the effect on the normal person of large doses of calcium chlorid taken by mouth. They found that there was marked increase in the output of ammonia in the urine, and believed that the bicarbonate ion was replaced by the chlorin ion in the blood and possibly also in the tissues, and that a mild acidosis resulted. They thought it possible that the increased acidity brings the proteins of the blood and tissues nearer their iso-electric point and releases the cations which are held in Donnan equilibrium, causing a fall in osmotic pressure and a consequent loss of water. This hypothesis will not explain results such as we have secured with calcium lactate. Bowler and Walters,[9] in their experimental work on the intravenous injection of calcium chlorid, have also confirmed this marked diuretic action.

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5. Brelet, M.: L'action diurétique des sels de calcium, Gaz. d. hôp. **95**:905-906, 1922.

6. Krummenacher: Le traitement de la pleuresie avec épanchement par le chlorure de calcium, Ann. d. méd. **13**:204-242 (March) 1923.

7. Atchley, D. W.; Loeb, R. F., and Benedict, E. M.: Physicochemical Studies of Calcium Chlorid Diuresis, J. A. M. A. **80**:1643-1644 (June 2) 1923.

8. Haldane, J. B. S.; Hill, R., and Luck, J. M.: Calcium Chloride Acidosis, J. Physiol. **57**:301-306 (June) 1923.

9. Bowler, J. P., and Walters, W.: Clinical Results of Intravenous Injections of Calcium Chlorid, to be published.

Fischer [10] has emphasized the dehydrating action of various salts on the different tissue colloids of the body. Some of the results following administration of these large doses of calcium might possibly be interpreted in the light of his general theory of the dehydrating action of large amounts of salt.

We are here reporting seven cases of edema in which calcium was used. Our first observations were made in September, 1922. Because Bowler and Walters had found that administration of large doses of calcium intravenously resulted in toxic symptoms, we did not use the doses recommended in the literature, but much smaller ones, with not very satisfactory results. The results of Bowler and Walters apparently do not apply to large doses of calcium given by mouth. In April, 1923, we gave calcium in large doses for the first time, in a case of very resistant diabetic edema. The results were spectacular.

REPORT OF CASES

CASE 1.—*History.*—A man, aged 43, came to the Mayo Clinic, March 30, 1923, for treatment with insulin. He had had glycosuria for fourteen months, with duodenal ulcer, for which a gastro-enterostomy had been performed at the clinic. He had been under dietary management for diabetes at the clinic, and had returned home. In the interim, he had become somewhat discouraged, and had not paid close attention to his diet. The details of his stay in the hospital may be noted in Chart 1 and Table 1.

Treatment and Course.—The patient's weight rose from 129 to 187 pounds (58.6 to 85 kg.) in seventeen days. At the beginning of the second period (Chart 1), treatment with insulin was started, and the diet and insulin dosage were maintained with little change throughout his stay in the hospital. The urine was practically sugar free at all times. In the third and fourth period, an attempt was made to control edema by the Karrell diet, by a dry diet very low in salt, and by magnesium sulphate given three times a day. Instead of reducing in weight, he actually gained during this time. The urine output was persistently low. April 16, calcium lactate was started (6 gm. a day). The first dose was given at noon. During the afternoon and evening, a moderate diuresis appeared for the first time, and for this twenty-four hour period, the urinary output was more than twice that of any day in the preceding week. On the second day, the patient had a little diarrhea, and the urine output diminished, although the enormous doses of magnesium sulphate given previously had not caused this. During the fifth, sixth and seventh periods, the calcium lactate was gradually increased until the patient was receiving 12 gm. a day. The urine output increased markedly, and the weight fell rapidly. In the eighth period, the calcium was stopped in order to determine positively whether the diuretic effect was due to the calcium. In this three-day period, the diuresis was checked, and the weight remained constant, while the nitrogen balance of the patient, for some unknown reason, became negative. Jansen [11] has shown, in a metabolic study of famine edema, that most cases appear to have a negative nitrogen balance. With the exception of the three-day period, this was not true in this case. When administration of calcium was resumed in the ninth

10. Fischer, M.: Oedema and Nephritis. Ed. 2. New York, John Wiley & Sons, 1915.

11. Jansen, W. H.: Die Ödemkrankheit, Deutsch. Arch. f. klin. Med. **131:** 144-200 (Feb.) 330-370 (March) 1920.

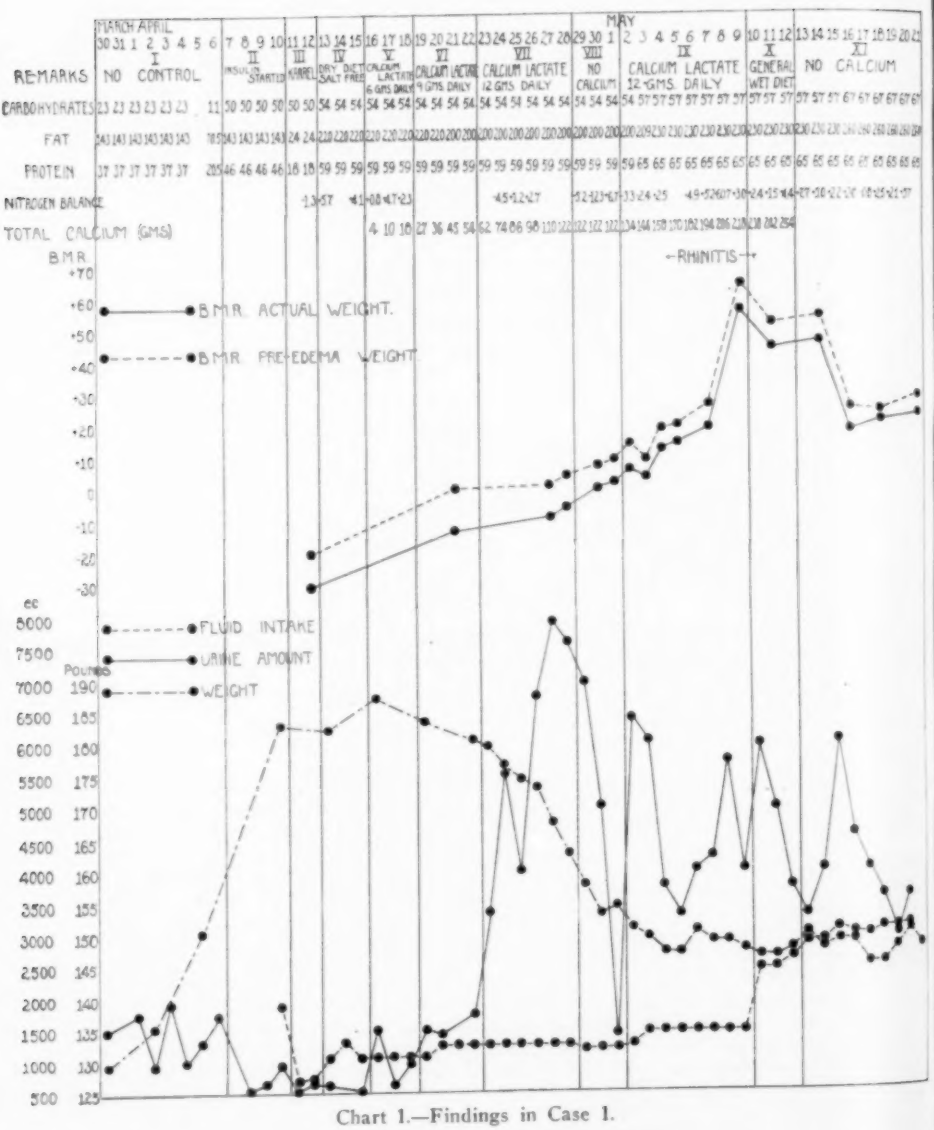

Chart 1.—Findings in Case 1.

period, loss of weight and diuresis reappeared. In the tenth period, the patient was allowed his regular diet, which contained a great deal of water, and the calcium was also continued. In the eleventh period, the calcium was discontinued and the patient was kept under observation, but edema did not recur. He was dismissed from the clinic, May 21, and has not had a recurrence of edema for five months.

TABLE 1.—*Effect of Calcium in Diabetes Mellitus with Edema (Case 1; a Man, Aged 43, height, 5 Feet 9¾ Inches)*

Date	Weight, Pounds	Fluid Intake, C.c	Urine, C.c.	Basal Metabolic Rate Calculated on Preedema Weight	Basal Metabolic Rate Calculated on Actual Weight
3/30/23	129.5	.....	1,500	.....	.....
4/ 1/23	.....	.....	1,750	.....	.....
4/ 2/23	135.5	.....	850	.....	.....
4/ 3/23	.....	.....	1,950	.....	.....
4/ 4/23	.....	.....	1,000	.....	.....
4/ 5/23	150.5	.....	1,300	.....	.....
4/ 6/23	.....	.....	1,700	.....	.....
4/ 8/23	.....	.....	550	.....	.....
4/ 9/23	.....	.....	600	.....	.....
4/10/23	183	1,800	900	.....	.....
4/11/23	.....	631	550	.....	.....
4/12/23	.....	631	600	—20	—32
4/13/23	182	1,076	575	.....	.....
4/14/23	.....	1,354	.....	.....	.....
4/15/23	.....	1,160	500	.....	.....
4/16/23	187	1,160	1,500	.....	.....
4/17/23	.....	1,160	600	.....	.....
4/18/23	.....	1,160	950	.....	.....
4/19/23	183.5	1,160	1,500	.....	.....
4/20/23	.....	1,248	1,400	.....	.....
4/21/23	.....	1,248	.....	0	—13
4/22/23	180	1,248	1,750	.....	.....
4/23/23	179.5	1,248	3,300	.....	.....
4/24/23	176	1,248	5,500	.....	.....
4/25/23	174.5	1,248	4,000	.....	.....
4/26/23	172.5	1,248	6,750	.....	.....
4/27/23	167.5	1,248	7,900	0 + 4	—11 — 8
4/28/23	162.5	1,248	7,600	+ 3 + 4	— 7 — 5
4/29/23	157.5	1,198	6,700	....	....
4/30/23	153	1,198	5,000	+ 8 + 7	+ 1 0
5/ 1/23	154	1,198	1,400	+ 9 + 9	+ 2 + 2
5/ 2/23	151	1,232	6,350	+13 +12	+ 5 + 6
5/ 3/23	149.5	1,449	6,000	+ 8 + 9	+ 2 + 3
5/ 4/23	147	1,449	3,700	+19 +17	+13 +10
5/ 5/23	147	1,449	3,300	+21 +20	+15 +14
5/ 6/23	151	1,449	4,000	....	....
5/ 7/23	148	1,449	4,200	+28 +25	+18 +21
5/ 8/23	148	1,449	5,700	....	....
5/ 9/23	147	1,449	4,000	+70 +60	+61 +52
5/10/23	146.5	2,407	5,900	....	....
5/11/23	146	2,407	4,900	+51 +55	+43 +47
5/12/23	147	2,007	3,700	....	....
5/13/23	150	2,801	3,300	....	....
5/14/23	147	3,057	4,000	+53 +58	+44 +49
5/15/23	148	2,872	6,000	....	....
5/16/23	148	2,872	4,000	+23 +29	+16 +21
5/17/23	145.5	2,872	4,000	....	....
5/18/23	145	3,072	3,600	+25 +27	+20 +22
5/19/23	147.5	3,072	2,800	....	....
5/20/23	150	3,072	3,000	....	....
5/21/23	147	.....	.....	+25 +33	+19 +27

The figures for fluid intake (Table 1) may seem a little high, but this is because they were calculated to include the water in the food and the water of metabolism besides the actual fluid intake.

Studies on the Chemistry of the Blood.—A few chemical studies were made (Table 2). There was no acidosis. The serum calcium was not increased by calcium treatment. These two readings are no indication, however, of what was going on during the period of the elevation of the metabolic rate, since they were taken prior to that time. A twenty-four hour electrolyte partition of the

blood and urine was made, but showed nothing of especial significance. Blood volume and concentration studies were also made (Table 3). During the height of the edema, the blood showed considerable concentration, and during the diuresis, a loss of solids with resulting dilution. This is in accordance with the findings of Brown and Rowntree[12] in certain cases of edema.

Basal Metabolic Rate.—One of the interesting points in this case is the change in the basal metabolic rate that followed the administration of calcium (Table 1). There was a marked increase during the period of calcium administration. There were no symptoms of hyperthyroidism, such as tachycardia, during this

TABLE 2.—*Blood Chemistry in Diabetic Edema Treated by Calcium Chlorid (Case 1)*

Date	Sugar, Mg.	Carbon Dioxid, per Cent.	Urea, Mg.	Uric Acid, Mg.	Creatinin, Mg.	Calcium, Mg.	Chlorin, Mg.	Sodium, Mg.	Amino-acid Nitrogen, Mg.
Period of Rising Edema:									
3/29	229	56	..	...	...	...	...	...	....
4/10	...	..	..	...	...	8.8	...	...	....
4/11	...	..	55	1.5	2.0	...	...	...	....
Period of Falling Edema:									
4/21	...	..	..	...	...	8.9	222	3.6	....
5/10	170	59	..	...	...	...	...	...	5.84
Urinalysis, Twenty-Four Hour Specimen:						Gm.	Gm.	Gm.	
4/20	...	..	..	...	...	0.25	3.4	5.3	

period, and the patient did not have goiter. The only suggestive features were an unusually good appetite and a slight tendency to night sweats. All readings, with the exception of the first two, were taken in duplicate, and as the technic was that of the usual routine in the Mayo Clinic, as described by Boothby and Sandiford, we have no reason to question their accuracy.

Discussion.—The cause of the consistent and marked rise in the basal metabolic rate toward the end of the period of calcium administration and as the edema was decreasing is unknown. Evidence possibly tending

TABLE 3.—*Hydremia Study (Case 1)*

Date	Plasma Volume: Total, C.c.	Plasma Volume: C.c. per Kg.*	Blood Volume: Total, C.c.	Blood Volume: C.c. per Kg.†	Hemoglobin (Palmer), per Cent.	Water in Whole Blood, per Cent.	Water in Plasma, per Cent.
Period of Rising Edema:							
4/10/23	3,600	43	6,000	72	132	78	93
Period of Falling Edema:							
5/12/23	4,493	64	6,418	91	99	85	92.3

* Normal value, 50 c.c. per kg.
† Normal value, 85 c.c. per kg.

to indicate that the increased metabolism was not due to the administration of calcium lactate was obtained by one of us, who took, with negative results, 259 gm. of calcium lactate over a two-week period at the rate of 18 gm. a day, and during the last five days was on a nephritic salt-free diet which contained less than 1 gm. of sodium chlorid (Table 4).

12. Brown, G. E., and Rowntree, L. G.: Volume and Composition of the Blood in Edema, to be published.

It is noteworthy that in this experiment on the normal subject the calcium content of the blood serum did not increase, nor was there any alteration observed in the electrocardiogram taken at the end of the period. Because of the evidence obtained in this experiment of a failure of absorption, or at least of no increased concentration in the blood, it is of no value in excluding the possible effect on the basal metabolic rate of raising the calcium content of the blood.

TABLE 4.—*Effect of Calcium on the Basal Metabolic Rate of a Normal Man (R. R., Aged 26, Height, 5 Feet 8¼ Inches)*

Date	Weight, Pounds	Pulse Rate	Respiratory Rate	Respiratory Quotient	Basal Metabolic Rate	Total Calcium Lactate Given, Gm.	Serum Calcium, Mg.
6/ 9/23	186½	70	15	0.82	—1	0	....
		70	12	0.81	—6	...	....
6/11/23	187½	79	14	0.82	+3	0	....
		80	13	0.83	+1	...	10.2
6/15/23	187	69	15	0.88	—2	43	....
		75	17	0.83	—2	...	....
6/18/23	188½	74	17	0.82	—4	97	....
		72	16	0.82	—5	...	....
6/20/23	187½	78	16	0.84	+2	133	11.8
		83	16	0.81	+3	...	....
6/25/23	186½	69	17	0.75	—4	223	....
		75	16	0.79	—6	...	....
6/27/23	185½	72	16	0.87	—1	259	10.9
		72	15	0.86	—2	...	....

TABLE 5.—*Effect of Calcium in a Case of Diabetes Mellitus with Edema (Case 2; a Man, Aged 32, Height 5 Feet 6¼ Inches)*

Date	Weight, Pounds	Fluid Intake, C.c	Urine Output, C.c.	Basal Metabolic Rate Calculated on Actual Weight		Basal Metabolic Rate Calculated on Preedema Weight		Total Calcium, Gm.
I. Period of Rising Edema:								
5/31/23	118	.....	2,600	....	....	....	....	...
6/ 1/23	...	.....	2,850	....	....	....	....	...
6/ 3/23	...	.....	3,200	....	....	....	....	...
6/ 4/23	125	.....	4,500	....	....	....	....	...
6/ 5/23	...	.....	3,600	....	....	....	....	...
6/ 6/23	...	.....	3,600	....	....	....	....	...
6/ 7/23	132.5	.....	2,850	....	....	....	....	...
6/10/23	...	.....	1,450	....	....	....	....	...
6/11/23	134.5	.....	2,100	....	....	....	....	...
6/12/23	137	2,981	1,550	—4	—8	+2	+2	...
6/13/23	137	3,271	2,500	....	....	....	....	...
II. Salt-free Dry Diet:								
6/14/23	137	1,172	1,550	....	....	....	....	...
6/15/23	136	1,372	1,400	—12	—14	—7	—9	...
6/16/23	134	1,472	1,000	....	....	....	....	...
III. Calcium Lactate (18 gm. daily):								
6/17/23	134	1,572	1,700	....	....	....	....	18
6/18/23	134	1,572	900	....	....	....	....	36
6/19/23	134	1,572	1,100	....	....	....	....	54
6/20/23	134	1,372	900	....	....	....	....	72
6/21/23	132.5	1,472	700	....	....	....	....	90
6/22/23	132.5	1,972	800	....	....	....	....	108

CASE 2.—A man, aged 32, weighing 118 pounds (53.6 kg.), who had had diabetes for a year and a half, following admission to the hospital, May 31, 1923, attained a weight of 137 pounds (62.2 kg.) in about twelve days. The details of his stay in the hospital are shown in Table 5. During the second period (Table 5), he was given a dry salt-free diet, but did not lose appreciably. In the third period, he was started on 18 gm. of calcium lactate daily, but this had no effect on his weight or urine output except for the gradual loss of a pound or two. In the fourth period, calcium chlorid in the same dosage was given. June 23,

because of trouble at home, he was forced to leave the hospital, although he still had edema. He took 18 gm. of calcium chlorid for a week at home, and then wrote that the edema had almost entirely disappeared and his weight had been reduced to 127.5 pounds (58 kg.). During his stay in the hospital, both the salt and the water intake was limited, and this regimen was continued, in part at least, at home.

Discussion.—Most of the observations on the effect of calcium on edema have been made with calcium chlorid. Blum discusses the relative advantages of calcium chlorid and calcium lactate. He believes that the chlorin ion is mainly excreted in the urine, and the calcium ion in the stool, so that more sodium will be driven from the body if the excess of chlorin is used, since the excretion of the chlorin ion by the kidney will carry sodium with it. In Atchley's case, considerable chlorid was excreted with ammonium, rather than with sodium, and this finding is confirmed in the work of Haldane, Hill and Luck. The acidosis caused by the large doses of chlorid given by these workers probably explains this discrepancy. Meyer and Cohn, in one experiment with calcium lactate, found an increase rather than a decrease in body weight.

Calcium chlorid is much more difficult to take than calcium lactate. Gastric distress, nausea, vomiting and diarrhea are not uncommon, although these can be avoided to some extent by giving the drug in capsule form. We believe, therefore, that calcium lactate should be tried first, and if this is not effective (as in two cases reported here), an attempt should be made to use the chlorid.

It must be remembered that in changing from the same dose of calcium lactate to calcium chlorid, the same amount of calcium is not being given. Because of the higher molecular weight, the percentage of calcium by weight in calcium lactate is 13 per cent.; while it is about 27 per cent. in the case of calcium chlorid (U.S.P.). Thus, in substituting calcium chlorid, we are increasing the dosage of calcium as well as adding the effect of the chlorin ion. All investigators observe cases which, for no known cause, are refractory to any form of calcium treatment.[13]

CASE 3.—A man, aged 41, who had moderately severe diabetes and severe acidosis, showed a plasma carbon dioxid capacity of 28 per cent. He was placed on restricted diet and insulin, and the acidosis gradually disappeared. In the course of sixteen days, his weight rose from 129 to 157.5 pounds (58.6 to 71.6 kg.), and there was considerable generalized edema visible (Chart 2). He

13. Since the foregoing was written, we have observed another patient with diabetes and edema. He was given 18 gm. of calcium lactate each day for three days, during which time his weight rose from 135 pounds to 143 pounds (from 61.2 to 64.9 kg.). Nine grams of calcium chlorid was substituted for five days, which would give approximately the same amount of calcium by weight daily as that in the lactate. Diuresis occurred promptly, and the patient's weight dropped from 143 to 129.5 pounds (61.2 to 58.5 kg.), and all vesicle edema disappeared. There was no restriction of water and salt during this time.

was then given large doses of calcium without restriction of his intake of water and salt. Calcium lactate was used first, and then, to hasten the process, a change was made to the same dosage of calcium chlorid. After fifteen days of calcium treatment, the visible edema had entirely subsided. The diet throughout consisted of carbohydrate, 40 gm., protein, 57 gm., and fat, 179 or 235 gm. About 40 units of insulin were used daily. The figures given for fluid intake in this case also include the water in the food, and the water of metabolism as well as the actual fluid intake.

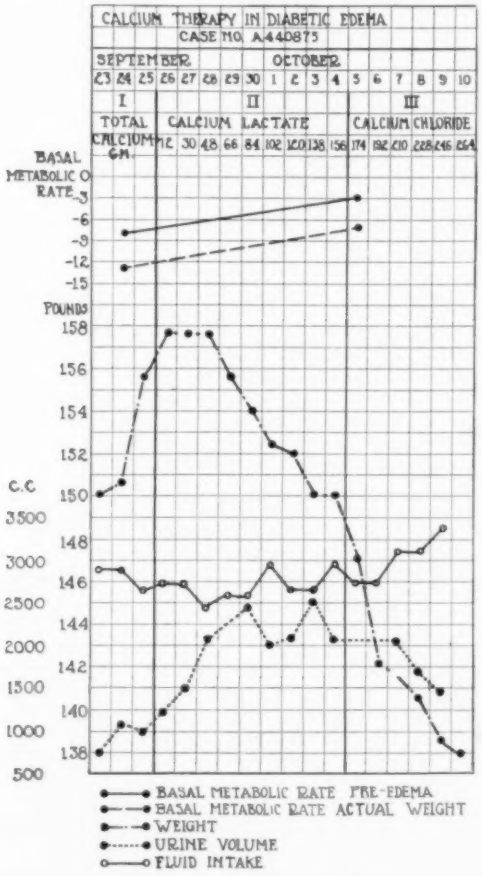

Chart 2.—Findings in Case 3.

Discussion.—The French observers especially have called attention to the necessity for coincidental restriction of salt and water in order to secure results with calcium. In this case, we attempted to determine whether calcium would have a diuretic action without any salt and water restriction. It did have a definite diuretic effect. Doubtless, the

coincidental limitation of salt and water aids the action of calcium in reducing edema. In certain cases, such restriction alone is sufficient to clear up edema. Nevertheless, it is evident from this observation that the diuretic action of calcium and its therapeutic effect on edema is sometimes independent of salt and water restriction.

It will be noted that the final weight of this patient, 138 pounds (62.7 kg.), was considerably above the initial weight of 129 pounds, although there was no visible edema. This discrepancy, we believe, is due to two causes, one a true gain of fat and muscle, the result of dietary treatment and administration of insulin, which, from our experience in previous cases of this type, we believe might have been from 5 to 10 pounds (2.2 to 4.4 kg.) and the other, a correction of initial dehydration. The rise in the basal metabolic rate we believe to be due to the improvement in nutrition.

CASE 4.—*History.*—A man, aged 58, came to the Mayo Clinic, Aug. 7, 1923, because of generalized edema and dyspnea.

Examination.—Typical chronic glomerular nephritis was found, which, according to the history, dated back to an upper respiratory tract infection seven months before. There was albumin 3 in the urine and many casts. The phenolsulphonephthalein test showed a 30 per cent. return. The blood urea was 37, the creatinin 2.3 and the uric acid 6.4 mg. for each hundred cubic centimeters. The systolic blood pressure was 160, the diastolic 100.

Treatment and Course.—The patient was placed on a diet of 40 gm. of protein which was salt-free, with restriction of fluids to 800 c.c., and 10 gm. of calcium lactate in powder form was administered daily by mouth. The clinical course during the period of hospitalization is shown in Chart 3. Edema disappeared rapidly, and was absent for the first time in three months. The blood pressure became normal in eight days and remained so. In thirteen days, the blood uric acid went down to 3.6 mg., the urea to 24 mg., and the creatinin to 1.2 mg. for each hundred cubic centimeters, while the urine showed only a trace of albumin and no casts. In fifteen days, the phenolsulphonephthalein output rose to 60 per cent. The effect of the calcium lactate seemed to wear away gradually, so that, by August 12 and 13, the diuresis was checked. As a result of administration of the same dose of calcium chlorid, however, diuresis occurred again, persisting until the weight was down to normal.

Second Admission.—The patient was well for two weeks after leaving the hospital. Then edema began to recur and gradually increased until he entered the hospital again, one month later, with a weight of 154 pounds (70 kg.). The administration of calcium chlorid, 18 gm. daily, was resumed, with restriction of salt and water. A marked diuresis again resulted, and the weight fell as much as 5 pounds (2.2 kg.) a day, reaching 118 pounds (53.6 kg.) the twenty-third day. On the second admission, the phenolsulphonephthalein output was 22 per cent. When the weight had returned to normal, it was 55 per cent.

Discussion.—The improvement of renal function after the reduction of edema is of especial interest in this case. Hülse called attention to this in connection with his use of calcium in war nephritis. He ascribed it to a possible action of calcium on the sympathetic nervous system, causing a relaxation of vascular spasm. It would seem to us more

plausible that edema of the kidney, coincident with the general edema, interferes with renal function, and that on the disappearance of this renal swelling, improvement in function occurs such as may be noted after decapsulation of the kidney, or in recovery from cardiac decompensation. In this case also, the advantage of calcium chlorid over the same dose of calcium lactate is evident from the fact that after the influence of the calcium lactate was no longer apparent, calcium chlorid was still effective.

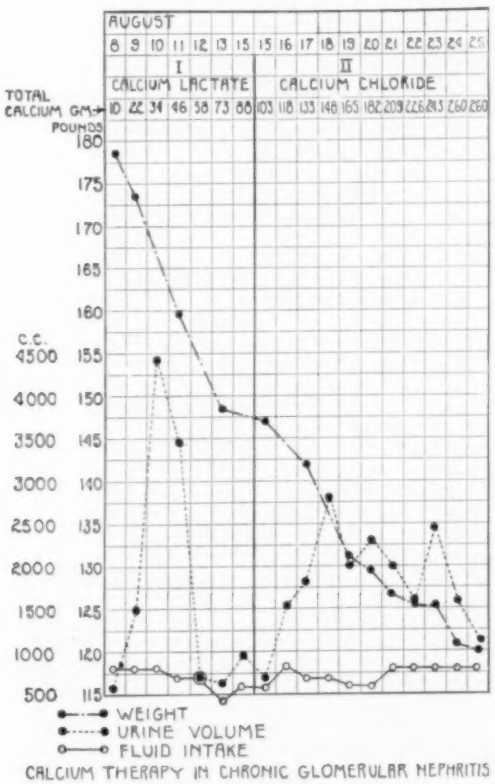

Chart 3.—Findings in Case 4.

Case 5.—A man, aged 37, came to the clinic with nephrosis and edema, which had been present intermittently for eighteen months, and continuously for two months. In spite of the administration of 18 gm. of calcium lactate for six days, and 18 gm. of calcium chlorid daily for six days more, there was no diuresis, although there was a gradual decline in weight from 188 to 167 pounds (85.4 to 76 kg.) in eighteen days. The salt and water intake were limited throughout the entire period, and frequent hot packs and sweats were given.

Discussion.—In this case, we cannot say that the calcium had any effect. The restriction of salt and water may have been responsible for the loss of weight. On the other hand, the hot packs and sweating may have obscured a tendency to a rise in urine output due to the calcium.

Case 6.—A youth, aged 19, came to the hospital because of nephritis which he had had since childhood, but more particularly because of generalized edema of one month's duration. He had chronic glomerular nephritis and general edema and was kept in the hospital for twenty-eight days (Chart 4). Salt was

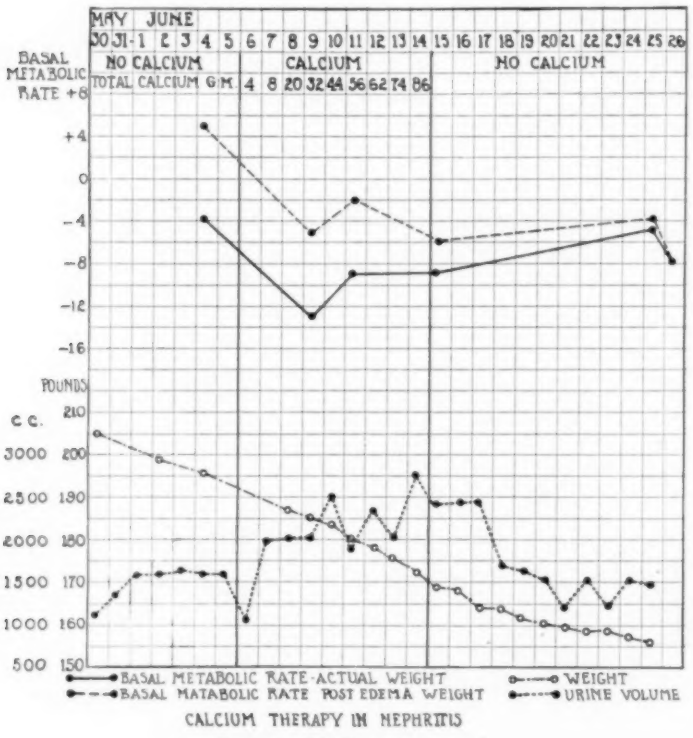

Chart 4.—Findings in Case 6.

restricted, and the daily fluid intake was limited to 800 c.c. throughout. Calcium lactate was also used, and the edema subsided completely. This patient returned to the hospital in three months with a rather marked nitrogen retention, which had not been present before. Despite this evidence of progressive nephritis, edema had not recurred.

Discussion.—In this case, we do not feel convinced that the drop in weight was due to the calcium alone, since this had started before calcium was tried. However, the diuretic effect of the calcium was marked

(Chart 4). The edema was lost without any significant variation in the basal metabolic rate.

Case 7.—*History.*—A man, aged 35, entered the clinic, May 21, 1923, because of edema, which he had had for about three months. His renal function, except for poor excretion of water and salt, was good, and a diagnosis of nephritis of the nephrosis type was made.

Treatment and Course.—The patient was kept on a low fluid intake for seven days with but 4 pounds (1.8 kg.) loss in weight, and with no diuresis or noticeable change in edema. He was then put on calcium lactate, 18 gm. a day, for

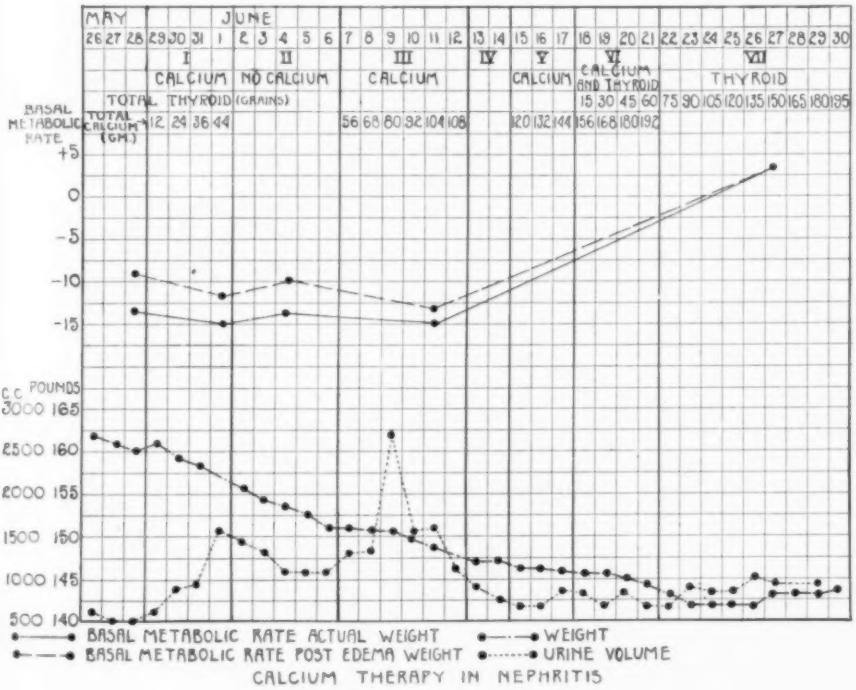

Chart 5.—Findings in Case 7.

periods of four days, with intervals between in which calcium was not given. In each period in which calcium was given, there was diuresis with loss of edema fluid, which stopped when the administration of calcium was discontinued. In thirty-one days, there was a loss of 20 pounds (9 kg.). The total dosage of calcium was 188 gm. The administration of thyroid extract in the sixth and seventh periods, while causing an elevation of the basal metabolic rate, did not increase the loss of water.

After the patient left the hospital, he was free from edema for a month. It then recurred slightly, following a cold and diarrhea. He was on a salt-free diet throughout, but this seemed to have no influence on his condition. He returned to the clinic in October, 1923, with a trace of edema about his ankles, and weighing 148.5 pounds (67.5 kg.). The edema was again controlled with calcium.

GENERAL COMMENT

Denis and Minot [14] and others have shown that the upper limit of serum calcium tends to be fixed, and that it seems to be impossible to raise it for any length of time in spite of the ingestion or injection of large amounts of calcium. This was true also in some of our cases. Our doses of calcium have been larger and were given over longer periods of time than any we can find in the literature in cases in which the serum calcium was also determined.

A summary of these data appears in Table 6.

Recent analyses show that milk contains from 0.99 gm. to 1.6 gm. of calcium for each liter, corresponding to from 7 to 12 gm. of calcium lactate for each liter. This makes average milk the equivalent of a 1 per cent. solution of calcium lactate. Milk has long been highly valued

TABLE 6.—*The Effect of Treatment with Calcium on the Serum Calcium*

Case	Diagnosis	Date	Total Calcium Salts Administered, Gm.	Total Calcium (Calculated) Gm.	Serum Calcium (Kramer-Tisdall) Mg. for Each 100 C.c.
	Normal	6/11/23	0	0	10.2
		6/20/23	133	17.2	11.8
		6/27/23	259	33.6	10.9
3	Diabetes	9/24/23	0	0	8.4
		10/ 8/23	228	39.6	9.3
1	Diabetes	4/10/23	0	0	8.8
		4/21/23	45	5.8	8.9
2	Diabetes	6/14/23	0	0	9.8
		6/20/23	72	9.3	10.5
6	Nephritis	6/ 1/23	0	0	9.0
		6/14/23	86	11.1	9.4
5	Nephrosis	10/ 4/23	0	0	10.7
		10/17/23	216	43.2	9.1
7	Nephrosis	5/25/23	0	0	9.2
		6/ 4/23	44	5.7	10.5
		6/14/23	108	14.0	9.7

in the treatment of acute nephritis. It has been used on more or less empiric grounds, and from the high protein and water content does not appear to be an ideal food when renal function is impaired. In the usual "milk cures," it is given in an amount of from 1 to 2 liters daily, and the calories in such amounts are insufficient to maintain nutrition, even with the patient in bed. The protein is from 30 to 40 gm. for each liter, which makes a diet consisting of two liters of milk rather richer in protein than is desirable in cases of nephritis with nitrogen retention, and salts other than calcium are present in not inconsiderable quantities. Some of the favorable effects ascribed to a milk diet in the past in such cases may therefore be due to the diuretic effect of the high calcium content. Bastedo [15] quotes Raphael, who studied the diuretic action of

14. Denis, W., and Minot, A. S.: Effects of Feeding with Calcium Salts on the Calcium Content of the Blood, J. Biol. Chem. **41**:357-361 (March) 1920.

15. Bastedo, W. A.: Materia Medica; Pharmacology; Therapeutics, Prescription Writing for Students and Practitioners, Philadelphia, W. B. Saunders Company, 1915.

various fluids and found that a liter of water caused a 100 per cent. increase in the urine output, while a liter of milk caused an increase of 153 per cent. If calcium is the cause of the beneficial action of milk diets in nephritis, it would seem logical to prescribe diets in which the protein, salt, fluid and caloric value have been properly adjusted, and then to give the necessary amount of calcium in addition, rather than to employ milk alone. It is possible that calcium in the combinations in which it is present in milk may be absorbed at a different rate than when it is given as the pure salt.

SUMMARY

We have tried the effect of large doses of calcium salts (from 12 to 18 gm. daily) in cases of massive edema of diabetic and nephritic origin. In six of seven cases, most of which had been resistant to other methods of treatment, edema disappeared completely. In one case, edema disappeared, but the part played by the calcium is questionable. In two cases of nephritis, edema recurred later. None of these cases were complicated by significant myocardial damage, and in none was any other diuretic given with the calcium. In the few instances in which we used small doses of calcium (from 1 to 3 gm. daily), little or no effect was observed. In some of the cases, edema was reduced by calcium lactate. In other cases, calcium chlorid seemed more effective. Large doses of calcium do not seem to increase the amount of serum calcium. In one case of chronic glomerular nephritis, renal function was definitely improved as the edema subsided. In one case of diabetic edema, the basal metabolic rate rose during the administration of calcium from — 13, April 21, to an average of + 57, May 9. A similar dose of calcium did not produce a change in the basal metabolic rate of a normal person. In the other cases of edema discussed, the administration of calcium had no effect on the basal metabolic rate. The high calcium content of milk may explain its diuretic action, and thus its popularity in the treatment of acute nephritis.

Book Reviews

BLOOD CHEMISTRY COLORIMETRIC METHODS. By WILLARD J. STONE. Price, $2.25. Pp. 71. New York: Paul B. Hoeber, 1923.

The author publishes in this book the methods of blood analysis devised by Folin and Wu, Benedict, Van Slyke, Myers, Bloor and others. To these are added instructions for conducting certain renal function tests with clincial comments on renal function. Brief dietary suggestions regarding the treatment of nephritis and diabetes complete the text. No claim of originality is made for any of the tests described, nor does the text carry with it a conviction that the author offers more than a compilation of certain laboratory tests which, in many other laboratory texts, are more comprehensively presented, or are described equally well as part of a general laboratory manual.

LECTURES ON ENDOCRINOLOGY. By WALTER TIMME, M. D., Attending Neurologist, Neurological Institute, New York; Professor of Endocrinology, Broad Street Hospital; Professor of Nervous and Mental Diseases, Polyclinic Medical School and Hospital. Price, $1.50. Pp. 123, with 27 illustrations. New York: Paul B. Hoeber, 1923.

This monograph is a reprint of an article published under the title of "Clinical Endocrinology" in 1921. It contains brief chapters on the thymus, pineal glands, the thyroids, the suprarenals, the pituitary, and the gonads. The pancreas and the parathyroid glands are not discussed. The treatment of this subject is clinical and the neurologic aspects of the several alleged endocrine syndromes are stressed. The author accepts, without much critical discussion many of the theories of pluri-glandular syndromes and mutual endocrine interaction. This may be necessary in such a brief paper, but may mislead a reader who accepts the book as a reliable authority. There is little evidence that the pineal body is an endocrine organ, and this applies to the thymus gland also.

The author assumes as a demonstrated fact a depression of thyroid activity by gonad hormones. "A good example of such hyperthyroidism is that seen in some women after the menopause—the ovarian function having ceased, the thyroid is left without sufficient counterbalance, and a hyperthyroid state ensues. This awakens over-activity of the adrenals with resulting high blood pressure." It is certain that spaying in animals below man produces no symptoms indicating hyperactivity of the thyroid, and neurocirculatory disturbances of the menopause have not yet been shown to be due to excessive thyroid secretion. The volume contains many such plausible statements that are not based on demonstrated facts. For instance—"During the period following menstruation there is usually a diminished thyroid activity."

The author promises an elaboration of the present theme in the near future. If, when this is done, he should combine his pleasing and easy style with greater critical discernment, he would do a distinct service to medical science in this difficult field.